National Cancer Institute
CARCINOGENESIS
Technical Report Series
NO. 121
1979

BIOASSAY OF DIMETHYL TEREPHTHALATE FOR POSSIBLE CARCINOGENICITY

CAS No. 120-61-6

NCI-CG-TR-121

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

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Carcinogenesis Testing Program
Division of Cancer Cause and Prevention
National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20205

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NIH Publication No. 79-1376

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FOREWORD: This report presents the results of the bioassay of dimethyl terephthalate conducted for the Carcinogenesis Testing Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland. This is one of a series of experiments designed to determine whether selected chemicals have the capacity to produce cancer in animals. A negative result, in which the test animals do not have a greater incidence of cancer than control animals, does not necessarily mean that the test chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of circumstances. A positive result demonstrates that the test chemical is carcinogenic for animals under the conditions of the test and indicates that exposure to the chemical is a potential risk to man. The actual determination of the risk to man from chemicals found to be carcinogenic in animals requires a wider analysis.

CONTRIBUTORS: This bioassay of dimethyl terephthalate was conducted by Hazleton Laboratories America, Inc. (1), Vienna, Virginia, initially under direct contract to NCI (2) and currently under a subcontract to Tracor Jitco, Inc. (3), Rockville, Maryland, prime contractor for the NCI Carcinogenesis Testing Program.

The principal investigators for the dimethyl terephthalate study were Drs. M. B. Powers (1) and R. W. Voelker (1). Drs. Powers, C. Cueto, Jr. (2), and O. G. Fitzhugh (3,4) were responsible for the selection of the doses administered during the chronic study. Ms. K. J. Petrovics (1) was responsible for data management and Mr. G. Najarian (1) for animal care. Histopathologic examinations were performed by Drs. D. A. Banas and R. H. Habermann (1) and reviewed by Dr. Voelker, and the diagnoses included in this report represent their interpretation.

Animal pathology tables and survival tables were compiled at EG&G Mason Research Institute (5). The statistical analyses were performed by Dr. J. R. Joiner (3) and Ms. P. L. Yong (3), using

methods selected for the bioassay program by Dr. J. J. Gart (6). Chemicals used in this bioassay were analyzed at Midwest Research Institute under the direction of Dr. E. Murrill (7), and feed mixtures containing the test chemical were analyzed at Hazleton Laboratories by Dr. C. L. Guyton and Mr. E. Missaghi. The results of these analyses were reviewed by Dr. C. W. Jameson (3).

This report was prepared at Tracor Jitco in collaboration with Hazleton Laboratories and NCI. Those responsible for the report at Tracor Jitco were Dr. C. R. Angel, Acting Director of the Bioassay Program; Dr. S. S. Olin, Deputy Director for Science; Dr. J. F. Robens, toxicologist; Dr. R. L. Schueler, pathologist; Dr. G. L. Miller, Ms. L. A. Owen, and Mr. W. D. Reichardt, bioscience writers; and Dr. E. W. Gunberg, technical editor, assisted by Ms. Y. E. Presley.

The following scientists at NCI were responsible for evaluating the bioassay experiment, interpreting the results, and reporting the findings: Dr. Kenneth C. Chu, Dr. Cipriano Cueto, Jr., Dr. J. Fielding Douglas, Dr. Richard A. Griesemer, Dr. Thomas E. Hamm, Dr. William V. Hartwell, Dr. Morton H. Levitt, Dr. Harry A. Milman, Dr. Thomas W. Orme, Dr. A. R. Patel, Dr. Sherman F. Stinson, Dr. Jerrold M. Ward, and Dr. Carrie E. Whitmire.

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SUMMARY

A bioassay of dimethyl terephthalate for possible carcinogenicity was conducted by administering the test chemical in feed to F344 rats and B6C3F1 mice.

Groups of 50 rats of each sex and 50 mice of each sex were administered dimethyl terephthalate at one of two doses, either 2,500 or 5,000 ppm, for 103 weeks, then observed for 2 additional weeks. Matched controls consisted of 50 untreated rats of each sex and 50 untreated mice of each sex. All surviving rats were killed at 105 or 106 weeks and all surviving mice at 104 or 105 weeks.

Administration of dimethyl terephthalate had no appreciable effect on the mean body weights of the rats and mice of either sex. No clinical signs related to administration of the test chemical were noted in the rats. Survivals of the rats and the mice at the end of the bioassay were not affected by the test chemical. Both species may have been able to tolerate higher doses.

In rats and mice of each sex, no tumors occurred at incidences that clearly were related to administration of the test chemical.

Although it is recognized that both rats and mice may not have received a dose of the test chemical sufficiently high to provide maximum test sensitivity, it is concluded that under the conditions of this bioassay, dimethyl terephthalate was not carcinogenic for F344 rats or B6C3F1 mice.

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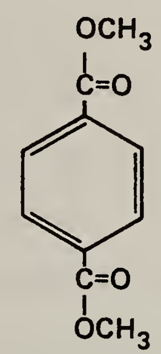
I. INTRODUCTION



Dimethyl terephthalate

Dimethyl terephthalate (CAS 120-61-6; NCI C50055) is one of the basic monomers used in the synthesis of polyester fibers (Dux, 1974; Goodman, 1965). The original process for the synthesis of synthetic fibers involved the alcoholysis of dimethyl terephthalate with ethylene glycol to form a linear polymer, polyethylene terephthalate (PET). This was then spun into a fiber given the trade name Terylene® by Imperial Chemical Industries, Ltd., in England. A comparable fiber, Dacron®, produced by Dupont in the United States, was obtained by reacting terephthalic acid with ethylene glycol (Moncrieff, 1970). Other PET fibers include Fortrel®, similar in composition to Dacron®, and Kodel®, a polymer of dimethyl terephthalate and 1,4-cyclohexanedimethanol (Moncrieff, 1970).

Today, terephthalic acid competes with dimethyl terephthalate as a starting material for these fibers, although the volume of production of the latter remains sizeable. In the United States,

production of dimethyl terephthalate, which was initiated in 1953, reached 145 million pounds per year in 1960 and 2.8 billion pounds per year in 1976 (Blackford, 1977).

More than 85% of dimethyl terephthalate is consumed in the manufacture of PET fibers for apparel, home furnishings, tire cord, ropes, sailcloth, and polyester fiberfill. In industry, these fibers are used as conveyer belts, in industrial laundries, for electrical fabrics, and for fire hose (Moncrieff, 1970). The second largest use of dimethyl terephthalate, which accounts for only 8% of the market, is in the manufacture of polyester film, used as photographic film, x-ray film, graphic arts film, and microfilm; computer, audio and video magnetic tape; and packaging. PET barrier resins are used for the manufacture of nonbreakable bottles for soft drinks (Blackford, 1977).

Dimethyl terephthalate polymerized with 1,4-butanediol yields a polybutylene terephthalate (PBT) resin. PBT resins are thermoplastic resins used in automobile ignition systems and in nonautomotive electrical and electronic connectors, switches, housings, machine gears, and injection-molded parts (Blackford, 1977). Finally, small quantities of dimethyl terephthalate are used directly as herbicide intermediates and in adhesives, printing inks, coatings, and paints (Towle et al., 1965).

The oral LD_{50} for dimethyl terephthalate has been reported as in excess of 6,500 mg/kg when the chemical was administered to male Long-Evans rats (Krasavage et al., 1973) and as greater than 3,200 mg/kg when the chemical was administered to rats of unspecified strain (Eastman Chemical Products, 1976). The oral LD_{50} in mice of unspecified strain also has been reported as greater than 3,200 mg/kg (Eastman Chemical Products, 1976). The chemical, administered in the diet to rats of unspecified strain at 50,000 ppm for 28 days, caused weight loss and high mortality (Fassett and Irish, 1963). The chemical caused a reduction in average body weight when administered in the diet to male Long-Evans rats at a dose of 10,000 ppm for 96 days, while doses of 5,000 and 2,500 ppm were without effect (Krasavage et al., 1973).

This monomer was selected for the Carcinogenesis Testing Program because of its large volume of production in the United States, and the resulting extensive human exposure of workers in the chemical industry.

II. MATERIALS AND METHODS

A. Chemical

Three lots of technical-grade dimethyl terephthalate, manufactured by Eastman Chemical Products, Inc., Kingsport, Tennessee, were obtained for use in these studies. Qualitative analyses of Lot No. B3A, used in the 90-day rat and mouse subchronic studies, were performed at Midwest Research Institute. The melting point was $142^{o}C$, which was consistent with the value of $141^{o}C$ given in the literature (Smith, 1921). Thin-layer chromatography indicated a slight impurity at the origin. A single homogeneous peak was obtained by vapor-phase chromatography. Elemental analyses were correct for $C_{10}H_{10}O_4$, the molecular formula of dimethyl terephthalate. The infrared, ultraviolet, visible, and nuclear magnetic resonance spectra were consistent with the spectra for dimethyl terephthalate in Sadtler Standard Spectra (Sadtler Research Laboratories, Philadelphia, Pa.). Similar results were obtained for Lot No. C4B, a white microcrystalline powder used in the 90-day rat subchronic studies and during weeks 0 to 52 of the rat chronic studies and weeks 0 to 53 of the mouse chronic studies.

The third lot of dimethyl terephthalate (Lot No. EC 2/27/76) was obtained in briquette form and was used during weeks 53 to 103 of the rat chronic studies and weeks 54 to 103 of the mouse chronic studies. Prior to use in the toxicity studies, this lot was ground to a powder and analyzed for identity and purity by Midwest Research Institute. The powdered material was found by thin-layer chromatography to be homogeneous. The melting point was 141 to 142°C, and results of elemental analyses agreed with theoretical values. One system of vapor-phase chromatography indicated a single, homogeneous peak, while a second system indicated a trace impurity of less than 0.01%. The infrared, ultraviolet, and nuclear magnetic resonance spectra were consistent with spectra given in Sadtler Standard Spectra.

The effects of heat on the stability of dimethyl terephthalate alone and the stability of a dimethyl terephthalate mix of 1:9 with animal meal were measured at Midwest Research Institute, using vapor-phase chromatography. The results of the heat stability analysis indicated that dimethyl terephthalate is stable under conditions of storage for at least 2 weeks at temperatures up to 60°C, and for the dosed feed mixtures theoretically containing 9.7% dimethyl terephthalate and stored at temperatures up to 45°C for 2 weeks, 10.1 $\pm$ 0.3% was recovered.

During the bioassay, the bulk chemical was stored at room temperature.

B. Dietary Preparation

The diet for each dosed group was prepared by mixing the amount of chemical required to achieve the desired dietary concentration with a small amount of the basal diet, Wayne® Lab-Blox Meal (Allied Mills, Inc., Chicago, Ill.), in a Waring blender. This premix was then combined with the remaining amount of basal diet required. Corn oil (Duke's® Corn Oil, C. F. Sauer Co., Richmond, Va.) equal to 2% of the final weight of feed was then added, primarily as a dust suppressant. This mixture was thoroughly mixed in a Patterson-Kelly twin-shell blender fitted with an intensifier bar. Control animals were administered basal diet containing 2% corn oil. Fresh diets were prepared once per week and stored at room temperature until used.

As a quality control check on the accuracy of the diet preparation and the homogeneity of the mixtures, the dimethyl terephthalate concentration was determined for randomly selected batches of formulated diet during the chronic studies. Results are summarized in Appendix G. At each dietary concentration, the

mean of the analytical concentrations for the checked samples was within 4.3% of the theoretical concentration, with a coefficient of variation of 5.7%.

C. Animals

F344 rats (Fischer) and B6C3F1 mice were obtained from the NCI Frederick Cancer Research Center, Frederick, Maryland, through contracts with the Division of Cancer Treatment, National Cancer Institute. Animals were quarantined for 14 days, determined to be free from observable disease or parasites, and assigned to dosed or control groups on the basis of initial individual body weights, so that a homogeneous distribution of mean weights and weight ranges was obtained between groups. At the beginning of the chronic studies, the rats were approximately 7 weeks old and the mice were approximately 8 weeks old.

D. Animal Maintenance

All animals were housed in rooms maintained at 20 to $24^{\circ}C$ and 45 to 55% relative humidity. Incoming air was filtered through 2-inch-thick disposable fiberglass filters at a rate that allowed

12 changes of room air per hour. Air was not recirculated. Fluorescent lighting was provided on a 12-hour-per-day cycle.

The rats and mice were initially housed five per cage in polycarbonate cages covered with stainless steel cage lids and non-woven fiber filter bonnets (Filtek, Appleton, Wis.). After 56 weeks, the male rats were divided two or three per cage to termination of the bioassay.

All cages were furnished with heat-treated hardwood chip bedding (Sani-chips®, Shurfire Products Corporation, Beltsville, Md.); the bedding was changed twice each week. Diets and well water were provided *ad libitum*.

Cages, water bottles, and sipper tubes were sanitized at 81°C twice per week, feed hoppers once per week, and cage racks once per month. An industrial dishwasher was used for the water bottles and sipper tubes; a cage and rack washer was used for the feed hoppers, cages, and racks. The detergent used in these washers was Acclaim® (Economics Laboratory, St. Paul, Minn.). When racks were washed, clean racks containing cages of animals were randomly repositioned in the room.

The rats and mice were housed in separate rooms. Control animals were housed in the same room as the respective dosed animals.

Prior to week 52 on study, the rats on the dimethyl terephthalate study were housed in the same room as rats on studies of the following chemicals:

Feed Studies

(CAS 119-53-9) benzoin
(CAS 13463-67-7) titanium dioxide
(CAS 89-78-1) dl-menthol

Gavage Studies

(CAS 7488-56-4) selenium disulfide
(CAS 127-69-5) sulfisoxazole
(CAS 108-60-1) bis(2-chloro-1-methylethyl) ether

Drinking Water Studies

(CAS 108-95-2) phenol

After week 52, the rats on the dimethyl terephthalate study were housed in the same room as rats on studies of selenium disulfide, sulfisoxazole, and phenol.

Mice on the dimethyl terephthalate study were housed in the same room as mice on studies of the following chemicals:

Feed Studies

(CAS 119-53-9) benzoin
(CAS 13463-67-7) titanium dioxide
(CAS 89-78-1) dl-menthol

Gavage Studies

(CAS 7488-56-4) selenium disulfide
(CAS 127-69-5) sulfisoxazole
(CAS 108-60-1) bis(2-chloro-1-methylethyl) ether

Drinking Water Studies

(CAS 108-95-2) phenol

E. Subchronic Studies

Subchronic feeding studies were conducted to establish the maximum tolerated doses of dimethyl terephthalate, on the basis of which two concentrations (referred to in this report as "low" and "high" doses) were selected for administration in the chronic studies. On the basis of the results of a 14-day range-finding study, doses of 1,750, 2,500, 5,000, 10,000 and 20,000 ppm were selected for administration in the subchronic studies. At each dose, 10 males and 10 females of each species were provided the test diets 7 days per week for 13 weeks, and control groups consisting of 10 males and 10 females of each species were fed basal diet containing 2% corn oil.

No compound-related effects were noted in the physical appearance, behavior, or food consumption of the rats or mice. All rats survived until the end of the study. Body weight gains

in males and females were unaffected by the test compound at doses of 1,750 to 5,000 ppm. At the end of the study, the body weight gain of males fed 10,000 ppm was 90% of the controls, and of those males fed 20,000 ppm was 83% of the controls. Mean body weight gain at the end of the study for females fed 10,000 ppm was 83% of the controls, and of those females fed 20,000 ppm was 71% of the controls.

Deaths in mice occurred in one male at 2,500 ppm, one male at 5,000 ppm, one male at 20,000 ppm, and two females at 20,000 ppm. There was no distinct effect of the test chemical on body weight gain in the mice at any dose.

No gross alterations related to the test chemical were noted in the dosed rats or mice at necropsy. Microscopically diffuse hepatic cell swelling in the livers was observed in rats and mice from all dosed groups. This finding was considered to be compound related but not dose related.

The low and high doses for the chronic studies were set at 2,500 and 5,000 ppm, respectively, for both the rats and the mice.

F. Chronic Studies

The designs of the chronic feeding studies in the rats and the mice are shown in tables 1 and 2.

G. Clinical and Pathologic Examinations

All animals were observed twice daily. Clinical signs and the presence of palpable masses were recorded every week. Mean body weights and food consumption were recorded every 2 weeks for the first 12 weeks and every month thereafter. Moribund animals and animals that survived to the end of the study were killed by exsanguination under sodium pentobarbital anesthesia (Diabutal®, Diamond Laboratories, Inc., Des Moines, Iowa) and necropsied.

The pathologic evaluation consisted of gross and microscopic examination of major tissues, major organs, and all gross lesions. The tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. The following tissues were examined microscopically: brain (frontal cortex and basal ganglia, parietal cortex and thalamus, and cerebellum and pons), pituitary, spinal cord (if

Table 1. Dimethyl Terephthalate Chronic Feeding Studies in Rats

Sex and Test Group	Initial No. of of Animals(a)	Dimethyl Terephthalate in Diet(b) (ppm)	Time on Study Dosed (weeks)	Time on Study Observed (weeks)
MALE				
Matched-Control	50	0		105-106
Low-Dose	50	2,500	103	2
High-Dose	50	5,000	103	2
FEMALE				
Matched-Control	50	0		106
Low-Dose	50	2,500	103	2
High-Dose	50	5,000	103	2

(a) Rats were approximately 7 weeks of age when placed on study.

(b) The test chemical was administered in a diet containing 2% corn oil. The control animals received only 2% corn oil in the diet. Diets were provided *ad libitum*.

Table 2. Dimethyl Terephthalate Chronic Feeding Studies in Mice

Sex and Test Group	Initial No. of of Animals (a)	Dimethyl Terephthalate in Diet (b) (ppm)	Time on Study Dosed (weeks)	Time on Study Observed (weeks)
MALE				
Matched-Control	50	0		104-105
Low-Dose	50	2,500	103	2
High-Dose	50	5,000	103	2
FEMALE				
Matched-Control	50	0		105
Low-Dose	50	2,500	103	2
High-Dose	50	5,000	103	2

(a) Mice were approximately 8 weeks of age when placed on study.

(b) The test chemical was administered in a diet containing 2% corn oil. The control animals received only 2% corn oil in the diet. Diets were provided *ad libitum*.

neurologic signs were present), eyes (if grossly abnormal), esophagus, trachea, salivary gland, mandibular lymph node, thyroid, parathyroid, heart, thymus, lungs and mainstem bronchi, liver, gallbladder (mice), pancreas, spleen, kidney, adrenal, stomach, small intestine, colon, urinary bladder, prostate or uterus, testes or ovaries, sternebrae, femur or vertebrae including marrow, mammary gland, tissue masses, and any unusual lesions.

Necropsies were also performed on all animals found dead, unless precluded in whole or in part by autolysis or cannibalization. Thus, the number of animals from which particular organs or tissues were examined microscopically varies, and does not necessarily represent the number of animals that were placed on study in each group.

H. Data Recording and Statistical Analyses

Pertinent data on this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, body weight, and

individual pathologic results, as recommended by the International Union Against Cancer (Berenblum, 1969). Data tables were generated for verification of data transcription and for statistical review.

These data were analyzed using the appropriate statistical techniques described in this section. Those analyses of the experimental results that bear on the possibility of carcinogenicity are discussed in the statistical narrative sections.

Probabilities of survival were estimated by the product-limit procedure of Kaplan and Meier (1958) and are presented in this report in the form of graphs. Animals were statistically censored as of the time that they died of other than natural causes or were found to be missing; animals dying from natural causes were not statistically censored. Statistical analyses for a possible dose-related effect on survival used the method of Cox (1972) for testing two groups for equality and Tarone's (1975) extensions of Cox's methods for testing for a dose-related trend. One-tailed P values have been reported for all tests except the departure from linearity test, which is only reported when its two-tailed P value is less than 0.05.

The incidence of neoplastic or nonneoplastic lesions has been given as the ratio of the number of animals bearing such lesions at a specific anatomic site (numerator) to the number of animals in which that site is examined (denominator). In most instances, the denominators included only those animals for which that site was examined histologically. However, when macroscopic examination was required to detect lesions prior to histologic sampling (e.g., skin or mammary tumors), or when lesions could have appeared at multiple sites (e.g., lymphomas), the denominators consist of the numbers of animals necropsied.

The purpose of the statistical analyses of tumor incidence is to determine whether animals receiving the test chemical developed a significantly higher proportion of tumors than did the control animals. As a part of these analyses, the one-tailed Fisher exact test (Cox, 1970) was used to compare the tumor incidence of a control group with that of a group of dosed animals at each dose level. When results for a number of dosed groups (k) are compared simultaneously with those for a control group, a correction to ensure an overall significance level of 0.05 may be made. The Bonferroni inequality (Miller, 1966) requires that the P value for any comparison be less than or equal to 0.05/k. In cases where this correction was used, it is discussed in the

narrative section. It is not, however, presented in the tables, where the Fisher exact P values are shown.

The Cochran-Armitage test for linear trend in proportions, with continuity correction (Armitage, 1971), was also used. Under the assumption of a linear trend, this test determines if the slope of the dose-response curve is different from zero at the one-tailed 0.05 level of significance. Unless otherwise noted, the direction of the significant trend is a positive dose relationship. This method also provides a two-tailed test of departure from linear trend.

A time-adjusted analysis was applied when numerous early deaths resulted from causes that were not associated with the formation of tumors. In this analysis, deaths that occurred before the first tumor was observed were excluded by basing the statistical tests on animals that survived at least 52 weeks, unless a tumor was found at the anatomic site of interest before week 52. When such an early tumor was found, comparisons were based exclusively on animals that survived at least as long as the animal in which the first tumor was found. Once this reduced set of data was obtained, the standard procedures for analyses of the incidence of tumors (Fisher exact tests, Cochran-Armitage tests, etc.) were followed.

When appropriate, life-table methods were used to analyze the incidence of tumors. Curves of the proportions surviving without an observed tumor were computed as in Saffiotti et al. (1972). The week during which an animal died naturally or was sacrificed was entered as the time point of tumor observation. Cox's methods of comparing these curves were used for two groups; Tarone's extension to testing for linear trend was used for three groups. The statistical tests for the incidence of tumors which used life-table methods were one-tailed and, unless otherwise noted, in the direction of a positive dose relationship. Significant departures from linearity (P less than 0.05, two-tailed test) were also noted.

The approximate 95 percent confidence interval for the relative risk of each dosed group compared to its control was calculated from the exact interval on the odds ratio (Gart, 1971). The relative risk is defined as p_t/p_c where p_t is the true binomial probability of the incidence of a specific type of tumor in a dosed group of animals and p_c is the true probability of the spontaneous incidence of the same type of tumor in a control group. The hypothesis of equality between the true proportion of a specific tumor in a dosed group and the proportion in a control group corresponds to a relative risk of unity. Values in excess

of unity represent the condition of a larger proportion in the dosed group than in the control.

The lower and upper limits of the confidence interval of the relative risk have been included in the tables of statistical analyses. The interpretation of the limits is that in approximately 95% of a large number of identical experiments, the true ratio of the risk in a dosed group of animals to that in a control group would be within the interval calculated from the experiment. When the lower limit of the confidence interval is greater than one, it can be inferred that a statistically significant result (P less than 0.025 one-tailed test when the control incidence is not zero, P less than 0.050 when the control incidence is zero) has occurred. When the lower limit is less than unity, but the upper limit is greater than unity, the lower limit indicates the absence of a significant result while the upper limit indicates that there is a theoretical possibility of the induction of tumors by the test chemical, which could not be detected under the conditions of this test.

III. RESULTS - RATS

A. Body Weights and Clinical Signs (Rats)

Administration of dimethyl terephthalate had no appreciable effect on the mean body weights of either the male or the female rats (figure 1). No clinical signs related to administration of the test chemical were observed.

Clinical signs involving the eyes were noted in both control and dosed animals throughout the course of the bioassay. The eyes were frequently pale, squinted, and lacrimating; the eyeballs were exophthalmic, and the corneas sometimes cloudy or opaque. Dark red crusted material was observed around the eyes. During the first year of the study, other clinical signs were noted infrequently and included a hunched and/or thin appearance, sores, soft feces, and a head tilt. The appearance and behavior of the rats during the second half of the study were characterized by signs of aging. Animals were frequently observed to be hunched and/or thin, to have sores on the body or extremities, and to have stains on the abdominal fur. Other signs noted less frequently were soft feces, a head tilt, abdominal distention, wheezing, dyspnea, decreased activity, a red discharge from the

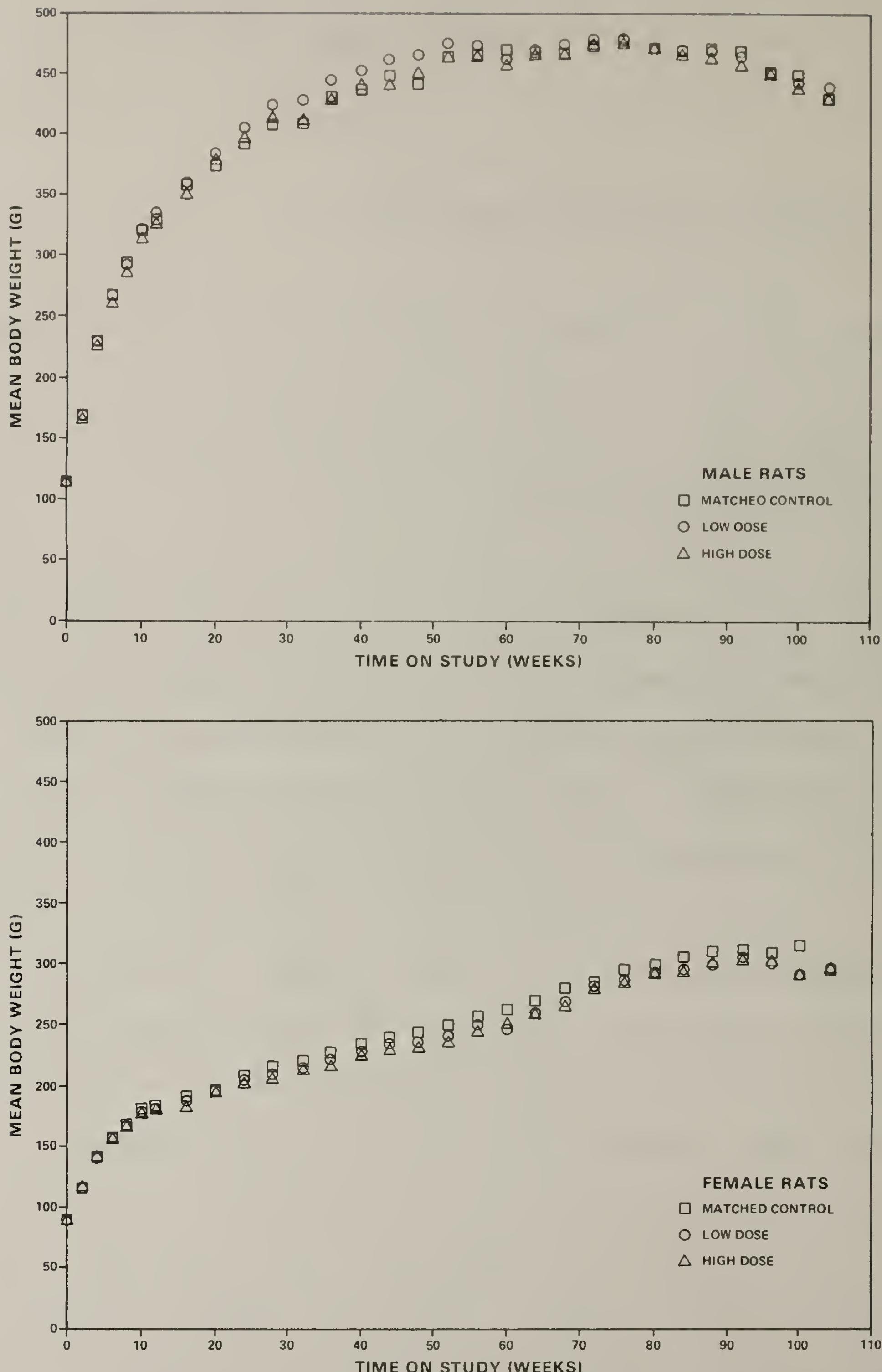


Figure 1. Growth Curves for Rats Administered Dimethyl Terephthalate in the Diet

nose, rough hair coats, paralysis, and swellings or discharges involving the urogenital area. Tissue masses, nodules, and wart-like lesions were noted more frequently in male than in female rats, and the incidence of these findings in dosed animals was lower than, or comparable to, incidences in control animals.

B. Survival (Rats)

The Kaplan and Meier curves estimating the probabilities of survival for male and female rats administered dimethyl terephthalate in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 2. The result of the Tarone test for positive dose-related trend in mortality is not significant in either sex.

In male rats, 41/50 (82%) of the high-dose group, 38/50 (76%) of the low-dose group, and 35/50 (70%) of the matched-control group lived to the end of the bioassay. In females, 38/50 (76%) of the high-dose group, 34/50 (68%) of the low-dose group, and 42/50 (84%) of the matched-control group lived to the end of the bioassay.

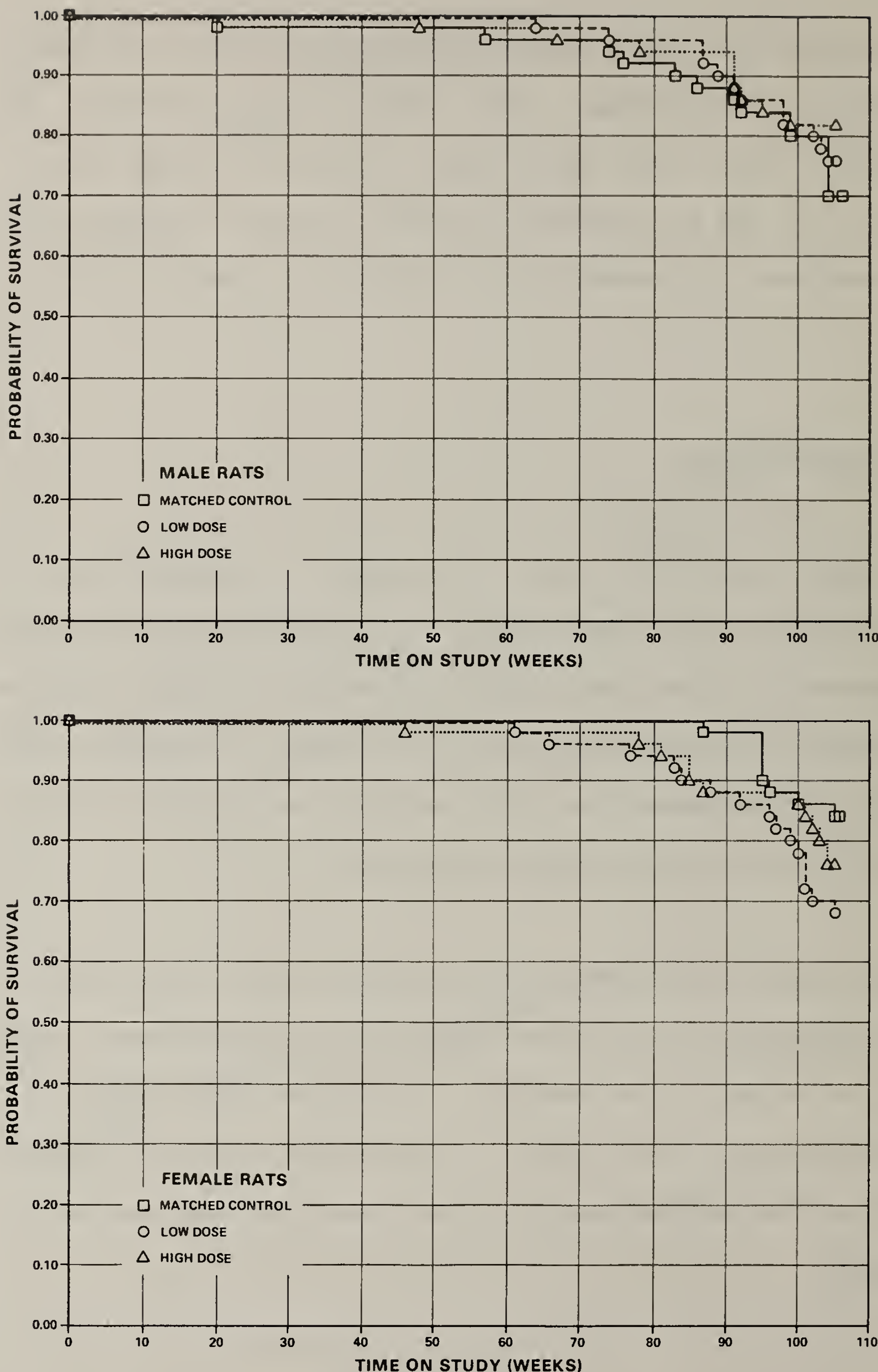


Figure 2. Survival Curves for Rats Administered Dimethyl Terephthalate in the Diet

Sufficient numbers of rats of each sex were at risk for the development of late-appearing tumors.

C. Pathology (Rats)

Histopathologic findings on neoplasms in rats are summarized in Appendix A, tables A1 and A2; findings on nonneoplastic lesions are summarized in Appendix C, tables C1 and C2.

A variety of tumors were observed in both control and dosed rats. Each of the tumor types observed has been encountered previously in aging F344 rats. These tumors occurred with no appreciable difference in frequency between control and dosed rats.

Degenerative, proliferative, and inflammatory lesions that occurred were similar in number and kind to those lesions commonly found in aged F344 rats.

Based on this histopathologic examination, there was no evidence for the carcinogenicity of dimethyl terephthalate for F344 rats under the conditions of this bioassay.

D. Statistical Analyses of Results (Rats)

Tables E1 and E2 in Appendix E contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

The results of the Cochran-Armitage test for positive dose-related trend in incidences of tumors and those of the Fisher exact test comparing the incidences in the dosed groups with those in the control group in the positive direction are not significant in either sex. For several tumors, the incidences in the control groups exceed those in the dosed groups.

In each of the 95% confidence intervals of relative risk, shown in the tables, the value of one or less than one is included; this indicates the absence of significant positive results. It should also be noted that each of the intervals (except that for the incidence of fibroma of the integumentary system in male rats, that for the incidence of pheochromocytoma of the adrenal in high-dose males, and that for the incidence of fibroadenoma of the mammary gland in high-dose females) has an upper limit greater than one, indicating the theoretical possibility of the

induction of tumors by dimethyl terephthalate, which could not be detected under the conditions of this test.

IV. RESULTS - MICE

A. Body Weights and Clinical Signs (Mice)

Administration of dimethyl terephthalate had no effect on the mean body weights of either the male or the female mice (figure 3).

Throughout the study, alopecia, usually involving the head, was observed more frequently in the dosed female mice than in the control female mice. Signs of fighting, such as sores, alopecia, and swollen, red, protruding, or enlarged testes, penis, or anus were observed more frequently in dosed male mice than in control male mice. Otherwise, the control and dosed groups of mice were comparable in appearance and behavior. The clinical signs, which increased in incidence as the mice aged, included thinness; a hunched appearance; abdominal distention; urine stains; decreased activity; swollen, lacrimating, opaque, cloudy, small, or protruding eyes; swelling of the neck, lower midline, inguinal region, or anus; rough hair coats; and tissue masses. The appearance of palpable nodules, tissue masses, and wart-like lesions did not appear to be related to the administration of the chemical.

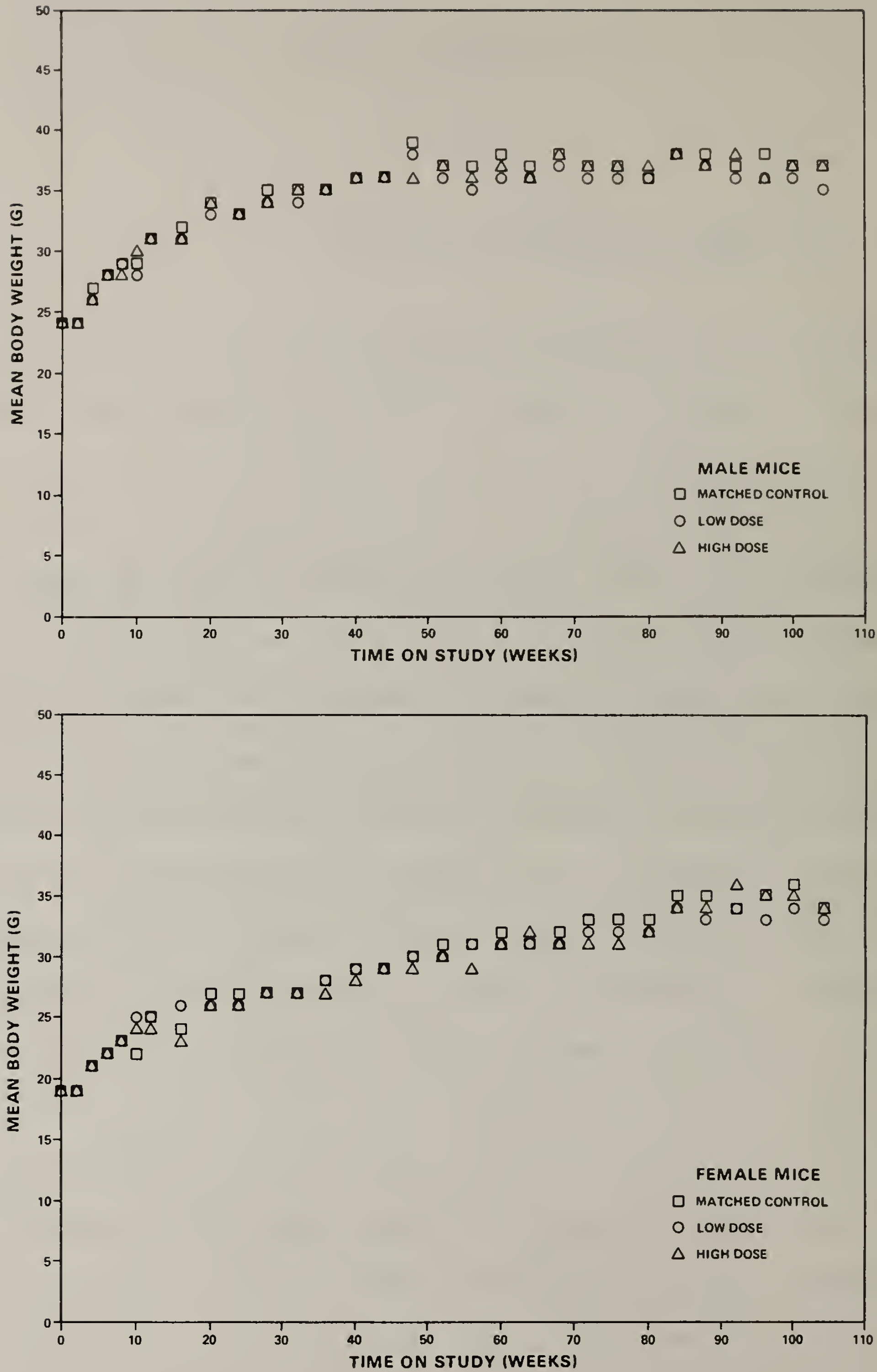


Figure 3. Growth Curves for Mice Administered Dimethyl Terephthalate in the Diet

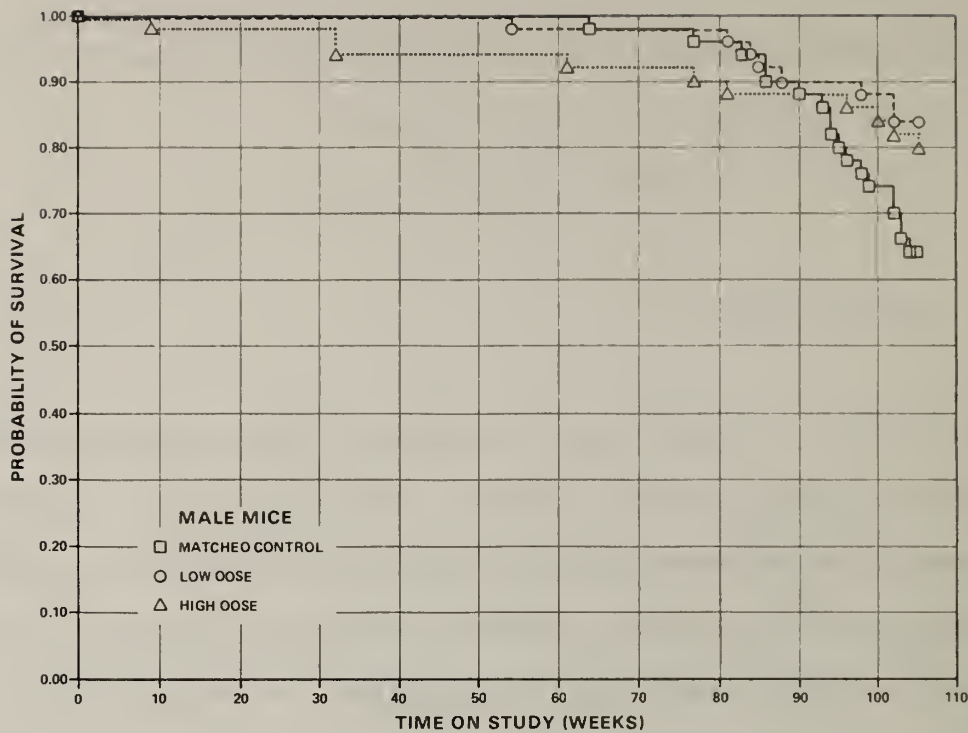
These findings were noted more frequently in male than in female mice, and increased in frequency with age.

B. Survival (Mice)

The Kaplan and Meier curves estimating the probabilities of survival for male and female mice administered dimethyl terephthalate in the diet at the doses of this bioassay, together with those of the matched controls, are shown in figure 4. The result of the Tarone test for positive dose-related trend in mortality is not significant in either sex.

In male mice, 39/50 (78%) of the high-dose group, 41/50 (82%) of the low-dose group, and 32/50 (64%) of the matched-control group lived to the end of the bioassay. In females, 34/50 (64%) of the high-dose group, 42/50 (84%) of the low-dose group, and 35/50 (70%) of the matched-control group lived to the end of the bioassay.

Sufficient numbers of mice of each sex were at risk for the development of late-appearing tumors.



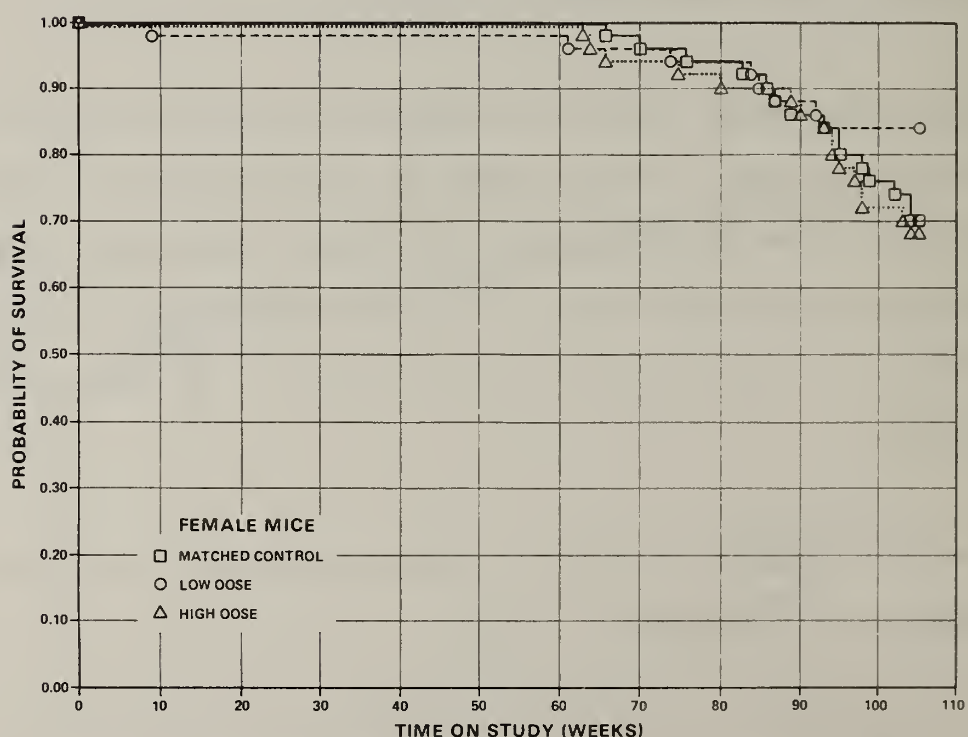


Figure 4. Survival Curves for Mice Administered Dimethyl Terephthalate in the Diet

C. Pathology (Mice)

Histopathologic findings on neoplasms in mice are summarized in Appendix B, tables B1 and B2; findings on nonneoplastic lesions are summarized in Appendix D, tables D1 and D2.

An increased incidence of primary lung tumors was observed in male B6C3F1 mice fed dimethyl terephthalate. Alveolar/bronchiolar adenomas or carcinomas were observed in 1/49 control males, 8/49 low-dose males, and 13/49 high-dose males. Alveolar/bronchiolar carcinomas were observed in 1/49 control males, 1/49 low-dose males, and 6/49 high-dose males. Alveolar/bronchiolar adenomas were usually small solitary lesions located in the subpleural area or immediately adjacent to a bronchiole. The cells involved were cuboidal to tall columnar and tended to be situated perpendicularly to the basement membrane in a single layer. These cells were arranged in complex papillary projections forming discrete nodules and compressing adjacent alveolar walls. Mitoses were rare.

Alveolar/bronchiolar carcinomas, however, were less discrete lesions and tended to be larger, occasionally multiple, or consisting of a confluence of two or more nodules. The individual cells tended to be less rigidly arranged along

basement membranes and were often piling up into multiple layers or arranged in solid sheets of cells without a papillary pattern. The cells often showed increased basophilia and a moderate mitotic index. Evidence of invasion into adjacent bronchioles, vessels, or surrounding lung parenchyma was frequently present.

In high-dose females, 27/49 mice developed malignant lymphoma, as compared with 16/48 control females. However, the occurrence of lymphomas in aged female B6C3F1 is quite variable and it appears unlikely that this increased incidence is related to compound administration, particularly as none of the low-dose females developed this neoplasm.

Other neoplasms observed were of the usual number and type observed in mice of this age and strain. Other degenerative, proliferative, and inflammatory lesions observed were also of the usual number and kind observed in aged B6C3F1 mice and were comparable in incidence between control and dosed mice.

Based on this histopathologic examination, a dose-related increase in primary tumors of the lung in male B6C3F1 mice may have been associated with long-term dietary administration of dimethyl terephthalate under the conditions of this bioassay.

D. Statistical Analyses of Results (Mice)

Tables F1 and F2 in Appendix F contain the statistical analyses of the incidences of those primary tumors that occurred in at least two animals of one group and at an incidence of at least 5% in one or more than one group.

In male mice, the result of the Cochran-Armitage test for positive dose-related trend in the incidence of alveolar/bronchiolar carcinomas is significant (P = 0.023), but the results of the Fisher exact test are not significant. The result of the Cochran-Armitage test for the combined incidence of alveolar/bronchiolar adenomas or carcinomas is significant (P = 0.001), and the Fisher exact test shows that the incidences in the low- and high-dose groups are significantly higher than that in the control group (P = 0.015 and P less than 0.001, respectively). Other male control groups concurrently occupying the same room as the mice in this study had incidences of alveolar/ bronchiolar adenomas and carcinomas of 5/49 (10%), 6/46 (13%), and 9/49 (18%), as compared with 1/49 (2%) in the dimethyl terephthalate matched controls.

From these results one may infer that the incidences of these tumors in the dimethyl terephthalate control group were

inordinately low. The highest incidence in the concurrent control groups exceeds that observed in the low dose animals in this study (8/49, 16%). Three of the 21 lesions among all of the controls were observed at 84, 95, and 96 weeks respectively, and the other 18 were seen later at 104 weeks.

If the incidence of 5/49 in one of the concurrent control groups is substituted for that of the matched controls in the present study, the Fisher exact test comparing this control group with the high dose (13/49, 27%) results in a probability level of P = 0.033. Using 6/46 as the incidence of the control group, the result is P = 0.082, and using 9/49 as the control incidence the result is P = 0.234. None of these results are statistically significant.

The variability evidenced by these control groups prevents an outright conclusion that the 13/49 (27%) incidence of lung tumors observed in the high dose male group in this study is associated with the administration of the chemical.

The result of the Cochran-Armitage test for dose-related trend in the incidence of lymphomas in female mice indicates a departure from linear trend (P less than 0.001) because the incidence of the tumor in the control group is greater than that in the

low-dose group. The Fisher exact comparison of the incidence of lymphomas in the high-dose group with that in the control group shows a P value of 0.025, which is at the 0.025 level required for significance when the Bonferroni inequality criterion is used for multiple comparison; however, the incidence in the low-dose group is significantly lower (P = 0.005) than that in the control group. Furthermore, in another concurrent control group at this laboratory (a 104-week study), the incidence of lymphoma and leukemia in female mice was 20/49 (40%).

A significant trend in the negative direction is observed in the incidence of hepatocellular carcinomas in female mice, in which the incidence in the control group exceeds the incidences in the dosed groups.

V. DISCUSSION

Administration of dimethyl terephthalate had no appreciable effect on the mean body weights or survivals of the rats and mice of either sex. Except for higher incidences of alopecia among dosed female mice and injuries due to fighting among dosed male mice, clinical signs in the rats and mice were associated with aging and were common to both dosed and control groups. Both species may have been able to tolerate higher doses. Dosed and control rats and mice of each sex survived long enough for the development of late-appearing tumors.

In the male and female rats, no tumors occurred in dosed groups at incidences that were significantly higher than those for corresponding control groups.

In the male mice, alveolar/bronchiolar adenomas or carcinomas occurred at incidences that were dose related, and in direct comparisons the incidences were significantly higher in the dosed groups than that in the matched-control group. The incidences of alveolar/bronchiolar adenomas or carcinomas and their variability in three other concurrent control groups of B6C3F1 mice did not permit the conclusion that the incidence of these tumors observed

in dosed male mice in this study was associated with the administration of the test chemical.

In the female mice, lymphomas occurred at incidences that were dose related; however, there was a departure from linear trend because the incidence in the control group was higher than that in the low-dose group. In direct comparisons, the incidence of the tumors in the high-dose group was higher than that in the control group. However, the P value for the high-dose group is just at the level required by the Bonferroni criterion (P = 0.025) when multiple comparisons are made, and a concurrent female control group held for a comparable length of time at the laboratory had an incidence of lymphoma and leukemia of 20/49 (40%). Thus, the occurrence of lymphomas in the dosed female B6C3F1 mice cannot clearly be related to the administration of the test chemical.

Although it is recognized that both rats and mice may not have received a dose of the test chemical sufficiently high to provide maximum test sensitivity, it is concluded that under the conditions of this bioassay, dimethyl terephthalate was not carcinogenic for F344 rats or B6C3F1 mice.

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APPENDIX A

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN

RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

TABLE A1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
SQUAMOUS CELL PAPILLOMA		3 (6%)	
SQUAMOUS CELL CARCINOMA	1 (2%)	2 (4%)	1 (2%)
TRICHOEPITHELIOMA	1 (2%)		
SEBACEOUS ADENOMA			1 (2%)
KERATOACANTHOMA	5 (10%)	3 (6%)	2 (4%)
FIBROMA		1 (2%)	
FIBROSARCOMA		1 (2%)	
HEMANGIOPERICYTOMA, NOS		1 (2%)	
*SUBCUT TISSUE	(50)	(49)	(49)
FIBROMA	8 (16%)		1 (2%)
FIBROSARCOMA		1 (2%)	1 (2%)
MESOTHELIOMA, METASTATIC			1 (2%)
HEMANGIOSARCOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(50)	(49)	(49)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)		2 (4%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	2 (4%)	
FIBROSARCOMA, METASTATIC		1 (2%)	
HEMANGIOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	1 (2%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		1 (2%)
MONOCYTIC LEUKEMIA	10 (20%)	13 (27%)	5 (10%)
#SPLEEN	(50)	(48)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(18)	(44)	(25)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(49)
ALVEOLAR/BRONCHIOLAR CA, METASTA		1 (2%)	
FIBROSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(48)
FIBROSARCOMA		1 (2%)	1 (2%)
#LIVER	(50)	(49)	(49)
NEOPLASTIC NODULE	2 (4%)		1 (2%)
HEPATOCELLULAR CARCINOMA	2 (4%)		
#SMALL INTESTINE	(49)	(49)	(49)
ADENOCARCINOMA, NOS	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
MIXED TUMOR, MALIGNANT	1 (2%)		
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(49)	(48)
CARCINOMA,NOS	1 (2%)		
CHROMOPHOBE ADENOMA	2 (4%)	6 (12%)	4 (8%)
#ADRENAL	(50)	(49)	(49)
CORTICAL ADENOMA	1 (2%)		
PHEOCHROMOCYTOMA	11 (22%)	6 (12%)	2 (4%)
#THYROID	(50)	(48)	(48)
FOLLICULAR-CELL ADENOMA		1 (2%)	
FOLLICULAR-CELL CARCINOMA		1 (2%)	
C-CELL ADENOMA	3 (6%)	1 (2%)	2 (4%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
C-CELL CARCINOMA		1 (2%)	3 (6%)
#PANCREATIC ISLETS	(50)	(49)	(49)
ISLET-CELL ADENOMA	5 (10%)	1 (2%)	1 (2%)
ISLET-CELL CARCINOMA	1 (2%)	1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
FIBROADENOMA			1 (2%)
*PREPUTIAL GLAND	(50)	(49)	(49)
CARCINOMA,NOS	6 (12%)	6 (12%)	3 (6%)
ADENOMA, NOS	1 (2%)		
#TESTIS	(49)	(49)	(49)
INTERSTITIAL-CELL TUMOR	44 (90%)	45 (9[illegible]%)	46 (94%)
NERVOUS SYSTEM			
#BRAIN	(50)	(49)	(49)
ASTROCYTOMA	1 (2%)	1 (2%)	
SPECIAL SENSE ORGANS			
*ZYMBAL'S GLAND	(50)	(49)	(49)
CARCINOMA,NOS	2 (4%)		2 (4%)
MUSCULOSKELETAL SYSTEM			
*RIB	(50)	(49)	(49)
FIBROSARCOMA, METASTATIC		1 (2%)	
BODY CAVITIES			
*PERITONEAL CAVITY	(50)	(49)	(49)
MESOTHELIOMA, MALIGNANT			1 (2%)
ALL OTHER SYSTEMS			
*MULTIPLE ORGANS	(50)	(49)	(49)
MESOTHELIOMA, NOS	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A1. MALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HEMANGIOSARCOMA	1 (2%)		
DIAPHRAGM			
FIBROSARCOMA, METASTATIC		1	
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	12	12	7
MORIBUND SACRIFICE	3		2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	35	38	41
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	48	49	49
TOTAL PRIMARY TUMORS	117	99	83
TOTAL ANIMALS WITH BENIGN TUMORS	46	46	48
TOTAL BENIGN TUMORS	82	67	62
TOTAL ANIMALS WITH MALIGNANT TUMORS	23	21	18
TOTAL MALIGNANT TUMORS	32	31	20
TOTAL ANIMALS WITH SECONDARY TUMORS#	1	2	1
TOTAL SECONDARY TUMORS	1	6	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT	3	1	1
TOTAL UNCERTAIN TUMORS	3	1	1
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
\# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE A2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
KERATOACANTHOMA	1 (2%)		
*SUBCUT TISSUE	(50)	(49)	(50)
FIBROMA	2 (4%)		
RESPIRATORY SYSTEM			
*NOSE	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
#LUNG	(50)	(49)	(50)
ALVEOLAR/BRONCHIOLAR ADENOMA	3 (6%)		
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(50)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)		
MONOCYTIC LEUKEMIA	7 (14%)	7 (14%)	3 (6%)
#MANDIBULAR L. NODE	(50)	(49)	(50)
HEMANGIOSARCOMA, INVASIVE		1 (2%)	
#CERVICAL LYMPH NODE	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA, METASTA			1 (2%)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
#MESENTERIC L. NODE	(50)	(49)	(50)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#THYMUS	(22)	(43)	(29)
ACINAR-CELL CARCINOMA, METASTATI			1 (3%)
CIRCULATORY SYSTEM			
NONE			
DIGESTIVE SYSTEM			
*TONGUE	(50)	(49)	(50)
SQUAMOUS CELL PAPILLOMA			1 (2%)
#SALIVARY GLAND	(50)	(47)	(50)
HEMANGIOSARCOMA		1 (2%)	
#LIVER	(50)	(49)	(50)
HEPATOCELLULAR CARCINOMA	1 (2%)	1 (2%)	
#PANCREAS	(49)	(49)	(50)
ACINAR-CELL CARCINOMA			1 (2%)
#STOMACH	(50)	(48)	(49)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
#COLON	(50)	(49)	(50)
HEMANGIOSARCOMA		1 (2%)	
URINARY SYSTEM			
#URINARY BLADDER	(48)	(46)	(45)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(46)	(48)
CHROMOPHOBE ADENOMA	21 (46%)	16 (35%)	19 (40%)
#ADRENAL	(49)	(49)	(49)
CORTICAL CARCINOMA			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
PHEOCHROMOCYTOMA	1 (2%)		
#THYROID	(50)	(49)	(50)
FOLLICULAR-CELL ADENOMA			1 (2%)
FOLLICULAR-CELL CARCINOMA			1 (2%)
C-CELL ADENOMA	1 (2%)	1 (2%)	
C-CELL CARCINOMA		2 (4%)	3 (6%)
#PANCREATIC ISLETS	(49)	(49)	(50)
ISLET-CELL ADENOMA			1 (2%)
ISLET-CELL CARCINOMA	1 (2%)		
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
ADENOMA, NOS		1 (2%)	
ADENOCARCINOMA, NOS	2 (4%)		
FIBROADENOMA	17 (34%)	12 (24%)	7 (14%)
*PREPUTIAL GLAND	(50)	(49)	(50)
CARCINOMA,NOS	1 (2%)	1 (2%)	1 (2%)
ADENOCARCINOMA, NOS	1 (2%)		
#UTERUS	(48)	(48)	(49)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
ENDOMETRIAL STROMAL POLYP	10 (21%)	10 (21%)	6 (12%)
ENDOMETRIAL STROMAL SARCOMA	1 (2%)	1 (2%)	2 (4%)
#OVARY	(48)	(48)	(48)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
NERVOUS SYSTEM			
#BRAIN	(49)	(49)	(50)
GLIOMA, NOS		1 (2%)	
ASTROCYTOMA		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE/CORNEA	(50)	(49)	(50)
SQUAMOUS CELL CARCINOMA			1 (2%)
MUSCULOSKELETAL SYSTEM			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE A2. FEMALE RATS: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
BODY CAVITIES			
*MESENTERY	(50)	(49)	(50)
ACINAR-CELL CARCINOMA, METASTATI			1 (2%)
ENDOMETRIAL STROMAL SARCOMA, MET			1 (2%)
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	8	16	12
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	42	34	38
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	38	38	29
TOTAL PRIMARY TUMORS	71	56	49
TOTAL ANIMALS WITH BENIGN TUMORS	36	30	23
TOTAL BENIGN TUMORS	56	40	35
TOTAL ANIMALS WITH MALIGNANT TUMORS	13	15	13
TOTAL MALIGNANT TUMORS	15	16	14
TOTAL ANIMALS WITH SECONDARY TUMORS#		1	4
TOTAL SECONDARY TUMORS		1	13
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX B

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN

MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

TABLE B1.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN MALE MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
FIBROMA	2 (4%)	2 (4%)	1 (2%)
FIBROSARCOMA		1 (2%)	1 (2%)
*SUBCUT TISSUE	(50)	(49)	(49)
FIBROMA	1 (2%)	3 (6%)	2 (4%)
FIBROSARCOMA	11 (22%)	7 (14%)	8 (16%)
FIBROUS HISTIOCYTOMA	1 (2%)		
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
HEPATOCELLULAR CARCINOMA, METAST	1 (2%)		1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	1 (2%)	7 (14%)	8 (16%)
ALVEOLAR/BRONCHIOLAR CARCINOMA	1 (2%)	1 (2%)	6 (12%)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
FIBROSARCOMA, METASTATIC	6 (12%)	1 (2%)	2 (4%)
RHABDOMYOSARCOMA, METASTATIC			1 (2%)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(50)	(49)	(49)
MALIG.LYMPHOMA, UNDIFFER-TYPE	1 (2%)		
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	1 (2%)	1 (2%)	3 (6%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	3 (6%)		
MALIGNANT LYMPHOMA, MIXED TYPE			1 (2%)
GRANULOCYTIC LEUKEMIA	1 (2%)		
#BONE MARROW	(49)	(49)	(49)
FIBROSARCOMA, METASTATIC	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#SPLEEN	(49)	(49)	(49)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
HEMANGIOSARCOMA	1 (2%)	1 (2%)	
#LYMPH NODE	(49)	(49)	(49)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
MALIGNANT LYMPHOMA, MIXED TYPE	1 (2%)		
#CERVICAL LYMPH NODE	(49)	(49)	(49)
RHABDOMYOSARCOMA, METASTATIC			1 (2%)
#BRONCHIAL LYMPH NODE	(49)	(49)	(49)
FIBROSARCOMA, METASTATIC			1 (2%)
#MESENTERIC L. NODE	(49)	(49)	(49)
HEMANGIOMA		2 (4%)	
#AXILLARY LYMPH NODE	(49)	(49)	(49)
FIBROSARCOMA, METASTATIC			1 (2%)
#THYMUS	(27)	(16)	(26)
FIBROSARCOMA, METASTATIC	1 (4%)	1 (6%)	1 (4%)
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(49)
FIBROSARCOMA, METASTATIC	1 (2%)		1 (2%)
RHABDOMYOSARCOMA			1 (2%)
HEMANGIOSARCOMA, METASTATIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(49)
HEPATOCELLULAR ADENOMA	2 (4%)		2 (4%)
HEPATOCELLULAR CARCINOMA	17 (35%)	13 (27%)	15 (31%)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
FIBROSARCOMA, METASTATIC	1 (2%)		1 (2%)
RHABDOMYOSARCOMA, METASTATIC			1 (2%)
HEMANGIOMA	1 (2%)		
HEMANGIOSARCOMA	1 (2%)	3 (6%)	
#PANCREAS	(49)	(49)	(49)
ACINAR-CELL CARCINOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#STOMACH	(49)	(49)	(49)
SQUAMOUS CELL PAPILLOMA	1 (2%)		
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(49)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
FIBROSARCOMA, METASTATIC			1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL	(48)	(47)	(48)
CORTICAL ADENOMA	1 (2%)		1 (2%)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
PHEOCHROMOCYTOMA		1 (2%)	
#THYROID	(48)	(47)	(47)
FOLLICULAR-CELL ADENOMA		1 (2%)	1 (2%)
#PANCREATIC ISLETS	(49)	(49)	(49)
ISLET-CELL ADENOMA	1 (2%)		1 (2%)
REPRODUCTIVE SYSTEM			
#PROSTATE	(47)	(48)	(49)
ACINAR-CELL CARCINOMA, METASTATI	1 (2%)		
HEMANGIOMA	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE/LACRIMAL GLAND	(50)	(49)	(49)
ADENOMA, NOS		1 (2%)	
*HARDERIAN GLAND	(50)	(49)	(49)
ADENOMA, NOS	1 (2%)	2 (4%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	18	8	10
MORIBUND SACRIFICE			
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	32	41	39
ANIMAL MISSING		1	1

@ INCLUDES AUTOLYZED ANIMALS

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B1. MALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	36	33	34
TOTAL PRIMARY TUMORS	52	46	51
TOTAL ANIMALS WITH BENIGN TUMORS	13	15	14
TOTAL BENIGN TUMORS	13	19	16
TOTAL ANIMALS WITH MALIGNANT TUMORS	30	25	27
TOTAL MALIGNANT TUMORS	39	27	35
TOTAL ANIMALS WITH SECONDARY TUMORS#	8	2	4
TOTAL SECONDARY TUMORS	19	4	12
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT			
TOTAL UNCERTAIN TUMORS			
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

TABLE B2.

SUMMARY OF THE INCIDENCE OF NEOPLASMS IN FEMALE MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	49
INTEGUMENTARY SYSTEM			
*SKIN	(48)	(50)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	
*SUBCUT TISSUE	(48)	(50)	(49)
FIBROSARCOMA	1 (2%)		1 (2%)
HEMANGIOSARCOMA			1 (2%)
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC	2 (4%)		1 (2%)
ALVEOLAR/BRONCHIOLAR ADENOMA	4 (8%)	4 (8%)	
ALVEOLAR/BRONCHIOLAR CARCINOMA		1 (2%)	
OSTEOSARCOMA, METASTATIC	1 (2%)		
HEMATOPOIETIC SYSTEM			
*MULTIPLE ORGANS	(48)	(50)	(49)
MALIGNANT LYMPHOMA, NOS		1 (2%)	1 (2%)
MALIG.LYMPHOMA, UNDIFFER-TYPE			1 (2%)
MALIG.LYMPHOMA, LYMPHOCYTIC TYPE	9 (19%)	4 (8%)	9 (18%)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	6 (13%)		15 (31%)
#SPLEEN	(48)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
HEMANGIOSARCOMA	1 (2%)		
#CERVICAL LYMPH NODE	(48)	(48)	(48)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
#MESENTERIC L. NODE	(48)	(48)	(48)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#LIVER	(48)	(50)	(49)
MALIG.LYMPHOMA, HISTIOCYTIC TYPE	1 (2%)		
#STOMACH	(48)	(49)	(49)
MAST-CELL TUMOR		1 (2%)	
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(48)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(49)
HEPATOCELLULAR CARCINOMA	5 (10%)	1 (2%)	
HEMANGIOSARCOMA		1 (2%)	
#STOMACH	(48)	(49)	(49)
SQUAMOUS CELL PAPILLOMA		1 (2%)	1 (2%)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
#SMALL INTESTINE	(48)	(50)	(49)
ADENOCARCINOMA, NOS, METASTATIC			1 (2%)
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(49)
TUBULAR-CELL ADENOCARCINOMA		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(44)	(49)
CHROMOPHOBE ADENOMA	3 (7%)	1 (2%)	1 (2%)
#ADRENAL	(48)	(50)	(49)
PHEOCHROMOCYTOMA	1 (2%)	2 (4%)	
#THYROID	(47)	(50)	(47)
FOLLICULAR-CELL ADENOMA	1 (2%)	1 (2%)	
#PANCREATIC ISLETS	(48)	(50)	(49)
ISLET-CELL ADENOMA	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(49)
ADENOMA, NOS	1 (2%)		
ADENOCARCINOMA, NOS	2 (4%)	2 (4%)	2 (4%)
#UTERUS	(47)	(50)	(49)
ADENOCARCINOMA, NOS			1 (2%)
ENDOMETRIAL STROMAL POLYP			2 (4%)
HEMANGIOSARCOMA		1 (2%)	1 (2%)
#OVARY	(47)	(50)	(48)
PAPILLARY CYSTADENOMA, NOS		3 (6%)	
NERVOUS SYSTEM			
#BRAIN	(48)	(50)	(49)
ASTROCYTOMA	1 (2%)		
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
NONE			
ALL OTHER SYSTEMS			
NONE			

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE B2. FEMALE MICE: NEOPLASMS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	50	50	50
NATURAL DEATH@	14	8	16
MORIBUND SACRIFICE	1		
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	35	42	34
ANIMAL MISSING			

@ INCLUDES AUTOLYZED ANIMALS

	CONTROL	LOW DOSE	HIGH DOSE
TUMOR SUMMARY			
TOTAL ANIMALS WITH PRIMARY TUMORS*	28	20	32
TOTAL PRIMARY TUMORS	37	26	37
TOTAL ANIMALS WITH BENIGN TUMORS	11	11	4
TOTAL BENIGN TUMORS	11	13	4
TOTAL ANIMALS WITH MALIGNANT TUMORS	24	11	31
TOTAL MALIGNANT TUMORS	26	12	33
TOTAL ANIMALS WITH SECONDARY TUMORS#	3		2
TOTAL SECONDARY TUMORS	3		6
TOTAL ANIMALS WITH TUMORS UNCERTAIN-BENIGN OR MALIGNANT		1	
TOTAL UNCERTAIN TUMORS		1	
TOTAL ANIMALS WITH TUMORS UNCERTAIN-PRIMARY OR METASTATIC			
TOTAL UNCERTAIN TUMORS			

* PRIMARY TUMORS: ALL TUMORS EXCEPT SECONDARY TUMORS
# SECONDARY TUMORS: METASTATIC TUMORS OR TUMORS INVASIVE INTO AN ADJACENT ORGAN

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

TABLE C1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
EPIDERMAL INCLUSION CYST		2 (4%)	
*SUBCUT TISSUE	(50)	(49)	(49)
NECROSIS, FAT	3 (6%)	1 (2%)	
RESPIRATORY SYSTEM			
#TRACHEA	(50)	(49)	(48)
PNEUMONIA, CHRONIC MURINE		1 (2%)	
#LUNG	(50)	(49)	(49)
EDEMA, NOS	1 (2%)		
INFLAMMATION, SUPPURATIVE			1 (2%)
PNEUMONIA, CHRONIC MURINE	9 (18%)	13 (27%)	15 (31%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
#LUNG/ALVEOLI	(50)	(49)	(49)
EPITHELIALIZATION	1 (2%)		
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(50)	(49)	(49)
PERIARTERITIS	1 (2%)		
HYPOPLASIA, HEMATOPOIETIC		1 (2%)	
#SPLEEN	(50)	(48)	(49)
ANGIECTASIS	1 (2%)		
HEMATOPOIESIS	2 (4%)		
#MESENTERIC L. NODE	(50)	(48)	(49)
LYMPHANGIECTASIS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(49)
FIBROSIS	39 (78%)	25 (51%)	45 (92%)
PERIARTERITIS			1 (2%)
#HEART/ATRIUM	(50)	(49)	(49)
THROMBOSIS, NOS	1 (2%)		
#MYOCARDIUM	(50)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
FIBROSIS	1 (2%)	14 (29%)	
DEGENERATION, NOS	43 (86%)	39 (80%)	45 (92%)
*AORTA	(50)	(49)	(49)
INFLAMMATION, NOS	1 (2%)		
DIGESTIVE SYSTEM			
#SALIVARY GLAND	(49)	(49)	(48)
CYST, NOS	1 (2%)		1 (2%)
INFLAMMATION, CHRONIC			1 (2%)
NECROSIS, FAT		1 (2%)	
#LIVER	(50)	(49)	(49)
HERNIA, NOS		2 (4%)	
INFLAMMATION, NOS		1 (2%)	
PELIOSIS HEPATIS		1 (2%)	
METAMORPHOSIS FATTY	1 (2%)	1 (2%)	
FOCAL CELLULAR CHANGE	1 (2%)	1 (2%)	1 (2%)
ANGIECTASIS		1 (2%)	
#BILE DUCT	(50)	(49)	(49)
HYPERPLASIA, NOS	1 (2%)	1 (2%)	
#PANCREAS	(50)	(49)	(49)
THROMBOSIS, NOS			1 (2%)
PERIARTERITIS			3 (6%)
ATROPHY, NOS			1 (2%)
#STOMACH	(50)	(49)	(49)
INFLAMMATION, NOS		1 (2%)	
ULCER, NOS			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ULCER, FOCAL	1 (2%)		
HYPERKERATOSIS			1 (2%)
ACANTHOSIS			1 (2%)
#COLON	(49)	(49)	(49)
NEMATODIASIS	3 (6%)	4 (8%)	4 (8%)
HYPERPLASIA, LYMPHOID		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(50)	(49)	(49)
PYELONEPHRITIS, NOS		1 (2%)	
INFLAMMATION, CHRONIC	38 (76%)	38 (78%)	27 (55%)
#URINARY BLADDER	(43)	(46)	(47)
HYPERPLASIA, EPITHELIAL		1 (2%)	
ENDOCRINE SYSTEM			
#PITUITARY	(48)	(49)	(48)
HYPERPLASIA, CHROMOPHOBE-CELL	1 (2%)		
#ADRENAL	(50)	(49)	(49)
DEGENERATION, LIPOID	1 (2%)		
ANGIECTASIS			1 (2%)
#ADRENAL MEDULLA	(50)	(49)	(49)
HYPERPLASIA, NOS	2 (4%)		1 (2%)
#THYROID	(50)	(48)	(48)
HYPERPLASIA, C-CELL		1 (2%)	1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(49)
LACTATION	1 (2%)		
#PROSTATE	(44)	(48)	(47)
INFLAMMATION, SUPPURATIVE	2 (5%)	1 (2%)	
#TESTIS	(49)	(49)	(49)
ATROPHY, NOS	4 (8%)	7 (14%)	3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
HYPOSPERMATOGENESIS		1 (2%)	
*EPIDIDYMIS	(50)	(49)	(49)
NECROSIS, FAT	2 (4%)	1 (2%)	1 (2%)
NERVOUS SYSTEM			
#BRAIN/MENINGES	(50)	(49)	(49)
ANGIECTASIS		1 (2%)	
#BRAIN	(50)	(49)	(49)
HYDROCEPHALUS, INTERNAL	1 (2%)		
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(49)
INFLAMMATION, NOS			1 (2%)
SYNECHIA, ANTERIOR		1 (2%)	
SYNECHIA, POSTERIOR			3 (6%)
CATARACT		4 (8%)	3 (6%)
*EYE/CORNEA	(50)	(49)	(49)
SCLEROSIS		1 (2%)	
VASCULARIZATION		1 (2%)	
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(49)	(49)
NECROSIS, FAT		1 (2%)	1 (2%)
*PERITONEAL CAVITY	(50)	(49)	(49)
NECROSIS, FAT		1 (2%)	
*MESENTERY	(50)	(49)	(49)
LYMPHANGIECTASIS		1 (2%)	
INFLAMMATION, CHRONIC		1 (2%)	
PERIARTERITIS	4 (8%)		3 (6%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C1. MALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
NECROSIS, FAT	4 (8%)	4 (8%)	6 (12%)
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
AUTOLYSIS/NO NECROPSY		1	1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	50	49	50
ANIMALS EXAMINED HISTOPATHOLOGICALLY	50	49	50
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(50)
HYPERKERATOSIS			1 (2%)
ACANTHOSIS			1 (2%)
*SUBCUT TISSUE	(50)	(49)	(50)
ABSCESS, NOS	1 (2%)		
NECROSIS, FAT	2 (4%)	2 (4%)	
RESPIRATORY SYSTEM			
#LUNG/BRONCHUS	(50)	(49)	(50)
HYPERPLASIA, LYMPHOID	1 (2%)		
#LUNG	(50)	(49)	(50)
CONGESTION, NOS		1 (2%)	
PNEUMONIA, CHRONIC MURINE	20 (40%)	11 (22%)	8 (16%)
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#SPLEEN	(49)	(49)	(49)
PHAGOCYTIC CELL			1 (2%)
HEMATOPOIESIS		1 (2%)	
#CERVICAL LYMPH NODE	(50)	(49)	(50)
INFLAMMATION, NOS	1 (2%)		
CIRCULATORY SYSTEM			
#HEART	(50)	(49)	(50)
MINERALIZATION		1 (2%)	

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
THROMBUS, ORGANIZED			1 (2%)
FIBROSIS	16 (32%)	30 (61%)	19 (38%)
#LEFT AURICULAR APPEN	(50)	(49)	(50)
THROMBUS, ORGANIZED		1 (2%)	
#MYOCARDIUM	(50)	(49)	(50)
FIBROSIS	9 (18%)		
DEGENERATION, NOS	25 (50%)	30 (61%)	19 (38%)
DIGESTIVE SYSTEM			
#LIVER	(50)	(49)	(50)
HERNIA, NOS	3 (6%)		2 (4%)
INFLAMMATION, NOS	1 (2%)		
NECROSIS, CENTRAL		2 (4%)	
METAMORPHOSIS FATTY	1 (2%)		2 (4%)
CYTOPLASMIC VACUOLIZATION	1 (2%)		
FOCAL CELLULAR CHANGE	4 (8%)	4 (8%)	1 (2%)
HEPATOCYTOMEGALY	1 (2%)		
ANGIECTASIS			1 (2%)
#BILE DUCT	(50)	(49)	(50)
HYPERPLASIA, NOS	1 (2%)		
#STOMACH	(50)	(48)	(49)
ULCER, NOS			1 (2%)
#COLON	(50)	(49)	(50)
NEMATODIASIS	1 (2%)	5 (10%)	8 (16%)
*RECTUM	(50)	(49)	(50)
NEMATODIASIS		1 (2%)	
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(50)
CALCULUS, NOS			1 (2%)
HYDRONEPHROSIS			1 (2%)
MULTIPLE CYSTS			1 (2%)
INFLAMMATION, CHRONIC	3 (6%)	5 (10%)	9 (18%)
#URINARY BLADDER	(48)	(46)	(45)
HYPERPLASIA, EPITHELIAL			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(46)	(48)
CYST, NOS	2 (4%)	1 (2%)	3 (6%)
MULTIPLE CYSTS			1 (2%)
ANGIECTASIS	1 (2%)	1 (2%)	1 (2%)
#ADRENAL	(49)	(49)	(49)
CYST, NOS		1 (2%)	
ANGIECTASIS	1 (2%)		
#THYROID	(50)	(49)	(50)
CYSTIC FOLLICLES		1 (2%)	
HYPERPLASIA, C-CELL	2 (4%)		1 (2%)
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(50)	(49)	(50)
GALACTOCELE	5 (10%)	2 (4%)	8 (16%)
INFLAMMATION, NOS			1 (2%)
LACTATION	7 (14%)	1 (2%)	9 (18%)
*VAGINA	(50)	(49)	(50)
PROLAPSE		1 (2%)	
#UTERUS	(48)	(48)	(49)
HYDROMETRA	3 (6%)	2 (4%)	2 (4%)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, FAT	2 (4%)		
#UTERUS/ENDOMETRIUM	(48)	(48)	(49)
HYPERPLASIA, CYSTIC	1 (2%)		
#OVARY	(48)	(48)	(48)
CYST, NOS		1 (2%)	3 (6%)
NECROSIS, FAT	1 (2%)		
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
*EYE	(50)	(49)	(50)
SYNECHIA, ANTERIOR	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE C2. FEMALE RATS: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SYNECHIA, POSTERIOR	1 (2%)	1 (2%)	2 (4%)
CATARACT	1 (2%)	1 (2%)	4 (8%)
*EYE/CORNEA	(50)	(49)	(50)
HYPERPLASIA, EPITHELIAL	1 (2%)		
VASCULARIZATION	2 (4%)		
*EYE/CONJUNCTIVA	(50)	(49)	(50)
INFLAMMATION, NOS	1 (2%)		
MUSCULOSKELETAL SYSTEM			
NONE			
BODY CAVITIES			
*ABDOMINAL CAVITY	(50)	(49)	(50)
NECROSIS, FAT	4 (8%)		7 (14%)
*PERITONEAL CAVITY	(50)	(49)	(50)
NECROSIS, FAT			1 (2%)
*MESENTERY	(50)	(49)	(50)
NECROSIS, FAT	1 (2%)	2 (4%)	1 (2%)
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
NECROSIS, FAT		1	
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	1	1	3
AUTOLYSIS/NO NECROPSY		1	

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS

IN MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

TABLE D1.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN MALE MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS MISSING		1	1
ANIMALS NECROPSIED	50	49	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	49	49	49
INTEGUMENTARY SYSTEM			
*SKIN	(50)	(49)	(49)
SEBACEOUS CYST		1 (2%)	
ULCER, NOS	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)	2 (4%)	4 (8%)
METAPLASIA, OSSEOUS			2 (4%)
*SUBCUT TISSUE	(50)	(49)	(49)
SEBACEOUS CYST		2 (4%)	
EDEMA, NOS			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
ABSCESS, NOS	1 (2%)	3 (6%)	
INFLAMMATION, CHRONIC	1 (2%)		
NECROSIS, FAT		1 (2%)	
RESPIRATORY SYSTEM			
#LUNG	(49)	(49)	(49)
CONGESTION, NOS	1 (2%)	1 (2%)	2 (4%)
HEMORRHAGE		1 (2%)	
INFLAMMATION, SUPPURATIVE	1 (2%)		1 (2%)
PNEUMONIA, CHRONIC MURINE	5 (10%)	6 (12%)	10 (20%)
HYPERPLASIA, ADENOMATOUS	1 (2%)		
HYPERPLASIA, ALVEOLAR EPITHELIUM		1 (2%)	
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(49)	(49)	(49)
HYPERPLASIA, HEMATOPOIETIC			2 (4%)
HYPERPLASIA, GRANULOCYTIC	1 (2%)		
#SPLEEN	(49)	(49)	(49)
CONGESTION, NOS	1 (2%)		

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ATROPHY, NOS	1 (2%)		
LEUKEMOID REACTION	1 (2%)		
HYPERPLASIA, LYMPHOID	6 (12%)	5 (10%)	4 (8%)
HEMATOPOIESIS	10 (20%)	4 (8%)	8 (16%)
#MESENTERIC L. NODE	(49)	(49)	(49)
LYMPHANGIECTASIS	1 (2%)		
CONGESTION, NOS	9 (18%)	7 (14%)	3 (6%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, NOS	1 (2%)		1 (2%)
HYPERPLASIA, LYMPHOID	8 (16%)	7 (14%)	10 (20%)
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(49)
THROMBOSIS, NOS		1 (2%)	
PERIARTERITIS	1 (2%)	1 (2%)	1 (2%)
#MYOCARDIUM	(48)	(49)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
INFLAMMATION, CHRONIC		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(49)	(49)	(49)
CYST, NOS			1 (2%)
THROMBOSIS, NOS	1 (2%)		1 (2%)
INFLAMMATION, NOS		1 (2%)	
NECROSIS, NOS	2 (4%)	3 (6%)	1 (2%)
NECROSIS, FOCAL	1 (2%)		3 (6%)
NECROSIS, COAGULATIVE	1 (2%)		
INFARCT, NOS	2 (4%)	4 (8%)	1 (2%)
HYPERPLASIA, FOCAL	2 (4%)		
HEMATOPOIESIS	1 (2%)		
*GALLBLADDER	(50)	(49)	(49)
INFLAMMATION, CHRONIC	1 (2%)		
#PANCREAS	(49)	(49)	(49)
FIBROSIS	1 (2%)		
PERIARTERITIS	2 (4%)		
#STOMACH	(49)	(49)	(49)
ULCER, FOCAL	1 (2%)		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#PEYERS PATCH	(49)	(49)	(49)
HYPERPLASIA, LYMPHOID		1 (2%)	
#DUODENUM	(49)	(49)	(49)
INFARCT, NOS			1 (2%)
#COLON	(49)	(48)	(49)
NEMATODIASIS	1 (2%)		5 (10%)
URINARY SYSTEM			
#KIDNEY	(49)	(49)	(49)
HYDRONEPHROSIS		1 (2%)	1 (2%)
HEMORRHAGE			1 (2%)
PYELONEPHRITIS, NOS			1 (2%)
PYELONEPHRITIS, ACUTE	1 (2%)		
INFLAMMATION, CHRONIC	2 (4%)	4 (8%)	11 (22%)
#URINARY BLADDER	(48)	(49)	(49)
INFLAMMATION, CHRONIC			2 (4%)
HYPERPLASIA, EPITHELIAL	1 (2%)		1 (2%)
ENDOCRINE SYSTEM			
#ADRENAL CORTEX	(48)	(47)	(48)
CYST, NOS	2 (4%)		
#ADRENAL MEDULLA	(48)	(47)	(48)
HYPERPLASIA, NOS	2 (4%)	2 (4%)	1 (2%)
#THYROID	(48)	(47)	(47)
HYPERPLASIA, FOLLICULAR-CELL	2 (4%)		
REPRODUCTIVE SYSTEM			
*PREPUTIAL GLAND	(50)	(49)	(49)
SEBACEOUS CYST		1 (2%)	
#PROSTATE	(47)	(48)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
*SEMINAL VESICLE	(50)	(49)	(49)
DISTENTION	2 (4%)	1 (2%)	

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#TESTIS	(18)	(49)	(45)
GRANULOMA, SPERMATIC	1 (6%)		1 (2%)
FIBROSIS	1 (6%)		
CALCIFICATION, NOS			1 (2%)
ATROPHY, NOS	1 (6%)	1 (2%)	3 (7%)
HYPOSPERMATOGENESIS		1 (2%)	1 (2%)
*EPIDIDYMIS	(50)	(49)	(49)
INFLAMMATION, NOS	1 (2%)		1 (2%)
GRANULOMA, SPERMATIC	1 (2%)		1 (2%)
NERVOUS SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
MUSCULOSKELETAL SYSTEM			
*VERTEBRAL COLUMN	(50)	(49)	(49)
OSTEOPHYTE	1 (2%)		
BODY CAVITIES			
*PERITONEUM	(50)	(49)	(49)
INFLAMMATION, NOS	2 (4%)		
*MESENTERY	(50)	(49)	(49)
THROMBOSIS, NOS			1 (2%)
PERIARTERITIS	1 (2%)		
NECROSIS, FAT	1 (2%)		
ALL OTHER SYSTEMS			
ADIPOSE TISSUE			
INFLAMMATION, CHRONIC			1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D1. MALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED	2	5	1
ANIMAL MISSING/NO NECROPSY		1	1
AUTO/NECROPSY/NO HISTO	1		

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2.

SUMMARY OF THE INCIDENCE OF NONNEOPLASTIC LESIONS IN FEMALE MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	50	50	50
ANIMALS NECROPSIED	48	50	49
ANIMALS EXAMINED HISTOPATHOLOGICALLY	48	50	49
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
#LUNG	(48)	(50)	(49)
CONGESTION, NOS	1 (2%)	2 (4%)	2 (4%)
HEMORRHAGE			1 (2%)
PNEUMONIA, ASPIRATION			1 (2%)
INFLAMMATION, SUPPURATIVE	1 (2%)		
PNEUMONIA, CHRONIC MURINE	4 (8%)	7 (14%)	5 (10%)
HEMATOPOIETIC SYSTEM			
#BONE MARROW	(48)	(50)	(49)
HYPERPLASIA, HEMATOPOIETIC	2 (4%)		
HYPERPLASIA, GRANULOCYTIC			1 (2%)
#SPLEEN	(48)	(50)	(49)
CONGESTION, NOS	1 (2%)		
ATROPHY, NOS	1 (2%)		1 (2%)
HYPERPLASIA, LYMPHOID	1 (2%)	8 (16%)	
HEMATOPOIESIS	5 (10%)	4 (8%)	2 (4%)
#MESENTERIC L. NODE	(48)	(48)	(48)
INFLAMMATION, CHRONIC	1 (2%)		
HYPERPLASIA, LYMPHOID	1 (2%)	4 (8%)	2 (4%)
CIRCULATORY SYSTEM			
#HEART	(48)	(49)	(48)
INFLAMMATION, CHRONIC		1 (2%)	

\# NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
#MYOCARDIUM	(48)	(49)	(48)
INFLAMMATION, NOS		1 (2%)	
DIGESTIVE SYSTEM			
#LIVER	(48)	(50)	(49)
CONGESTION, NOS	2 (4%)	1 (2%)	
NECROSIS, NOS	2 (4%)		
NECROSIS, FOCAL		1 (2%)	
INFARCT, NOS		1 (2%)	
FOCAL CELLULAR CHANGE		1 (2%)	
#BILE DUCT	(48)	(50)	(49)
FIBROSIS			1 (2%)
#PANCREAS	(48)	(50)	(49)
MINERALIZATION			1 (2%)
HEMORRHAGIC CYST	1 (2%)		
#PANCREATIC ACINUS	(48)	(50)	(49)
ATROPHY, NOS			1 (2%)
#STOMACH	(48)	(49)	(49)
ULCER, FOCAL	1 (2%)		
MASTOCYTOSIS	1 (2%)		
#PEYERS PATCH	(48)	(50)	(49)
HYPERPLASIA, LYMPHOID			3 (6%)
#COLON	(48)	(50)	(49)
NEMATODIASIS		2 (4%)	1 (2%)
URINARY SYSTEM			
#KIDNEY	(48)	(50)	(49)
HYDRONEPHROSIS		1 (2%)	1 (2%)
INFLAMMATION, CHRONIC	2 (4%)	3 (6%)	
INFARCT, NOS		2 (4%)	2 (4%)
#URINARY BLADDER	(46)	(49)	(46)
HEMORRHAGE			1 (2%)
INFLAMMATION, CHRONIC			1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ENDOCRINE SYSTEM			
#PITUITARY	(46)	(44)	(49)
HYPERPLASIA, CHROMOPHOBE-CELL			2 (4%)
#ADRENAL CORTEX	(48)	(50)	(49)
DEGENERATION, NOS		1 (2%)	
#ADRENAL MEDULLA	(48)	(50)	(49)
HYPERPLASIA, NOS		1 (2%)	
#THYROID	(47)	(50)	(47)
CYSTIC FOLLICLES	1 (2%)	2 (4%)	
HYPERPLASIA, FOLLICULAR-CELL	1 (2%)	1 (2%)	
REPRODUCTIVE SYSTEM			
*MAMMARY GLAND	(48)	(50)	(49)
LACTATION	2 (4%)	2 (4%)	3 (6%)
#UTERUS	(47)	(50)	(49)
HYDROMETRA	1 (2%)		
THROMBOSIS, NOS			1 (2%)
HEMORRHAGE	1 (2%)		
INFLAMMATION, CHRONIC	1 (2%)		
#UTERUS/ENDOMETRIUM	(47)	(50)	(49)
INFLAMMATION, SUPPURATIVE		1 (2%)	
HYPERPLASIA, CYSTIC	39 (83%)	39 (78%)	33 (67%)
#OVARY	(47)	(50)	(48)
FOLLICULAR CYST, NOS	5 (11%)	6 (12%)	5 (10%)
PAROVARIAN CYST	2 (4%)	4 (8%)	2 (4%)
HEMORRHAGIC CYST	5 (11%)		
NERVOUS SYSTEM			
#BRAIN/MENINGES	(48)	(50)	(49)
INFLAMMATION, NOS		1 (2%)	
SPECIAL SENSE ORGANS			
*EYE	(48)	(50)	(49)
INFLAMMATION, NOS	1 (2%)		1 (2%)

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

TABLE D2. FEMALE MICE: NONNEOPLASTIC LESIONS (CONTINUED)

	CONTROL	LOW DOSE	HIGH DOSE
ABSCESS, NOS	1 (2%)		
CATARACT			1 (2%)
MUSCULOSKELETAL SYSTEM			
*SKELETAL MUSCLE	(48)	(50)	(49)
CALCIFICATION, DYSTROPHIC		1 (2%)	
BODY CAVITIES			
*PERITONEUM	(48)	(50)	(49)
INFLAMMATION, SUPPURATIVE	1 (2%)		
*MESENTERY	(48)	(50)	(49)
PERIARTERITIS	1 (2%)		
ALL OTHER SYSTEMS			
NONE			
SPECIAL MORPHOLOGY SUMMARY			
NO LESION REPORTED		1	1
AUTOLYSIS/NO NECROPSY	2		1

NUMBER OF ANIMALS WITH TISSUE EXAMINED MICROSCOPICALLY
* NUMBER OF ANIMALS NECROPSIED

APPENDIX E

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN RATS ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Squamous-cell Papilloma of the Skin (b)	0/50 (0)	3/49 (6)	0/49 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.013		
Relative Risk (f)		Infinite	--
Lower Limit		0.614	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	105	--
Integumentary System: Keratoacanthoma of the Skin (b)	5/50 (10)	3/49 (6)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.612	0.408
Lower Limit		0.100	0.040
Upper Limit		2.967	2.358
Weeks to First Observed Tumor	83	105	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Skin tumors (b,g)	7/50 (14)	8/49 (16)	4/49 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.166	0.583
Lower Limit		0.401	0.133
Upper Limit		3.489	2.139
Weeks to First Observed Tumor	83	103	105
Integumentary System: Fibroma (b)	8/50 (16)	1/49 (2)	1/49 (2)
P Values (c,d)	P = 0.005 (N)	P = 0.017 (N)	P = 0.017 (N)
Relative Risk (f)		0.128	0.128
Lower Limit		0.003	0.003
Upper Limit		0.898	0.898
Weeks to First Observed Tumor	92	105	105

Table El. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	13/50 (26)	14/49 (29)	7/49 (14)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.099	0.549
Lower Limit		0.536	0.203
Upper Limit		2.266	1.348
Weeks to First Observed Tumor	20	64	48
Liver: Neoplastic Nodule or Hepatocellular Carcinoma (b)	4/50 (8)	0/49 (0)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.000	0.255
Lower Limit		0.000	0.005
Upper Limit		1.100	2.459
Weeks to First Observed Tumor	106	--	99

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	2/48 (4)	6/49 (12)	4/48 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.939	2.000
Lower Limit		0.558	0.302
Upper Limit		28.625	21.281
Weeks to First Observed Tumor	105	105	91
Adrenal: Pheochromocytoma (b)	11/50 (22)	6/49 (12)	2/49 (4)
P Values (c,d)	P = 0.006 (N)	N.S.	P = 0.008 (N)
Relative Risk (f)		0.557	0.186
Lower Limit		0.183	0.021
Upper Limit		1.505	0.793
Weeks to First Observed Tumor	76	87	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma or Adenoma (b)	3/50 (6)	2/48 (4)	4/48 (8)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.694	1.389
Lower Limit		0.060	0.248
Upper Limit		5.794	9.031
Weeks to First Observed Tumor	105	105	105
Pancreatic Islets: Islet-cell Carcinoma or Adenoma (b)	6/50 (12)	2/49 (4)	2/49 (4)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.340	0.340
Lower Limit		0.035	0.035
Upper Limit		1.793	1.793
Weeks to First Observed Tumor	86	105	105

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Preputial Gland: Carcinoma, NOS (b)	6/50 (12)	6/49 (12)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.020	0.510
Lower Limit		0.293	0.087
Upper Limit		3.556	2.243
Weeks to First Observed Tumor	83	87	91
Preputial Gland: Carcinoma, NOS, or Adenoma, NOS (b)	7/50 (14)	6/49 (12)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.875	0.437
Lower Limit		0.261	0.077
Upper Limit		2.820	1.793
Weeks to First Observed Tumor	83	87	91

Table E1. Analyses of the Incidence of Primary Tumors in Male Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Testis: Interstitial-cell Tumor (b)	44/49 (90)	45/49 (92)	46/49 (94)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.023	1.045
Lower Limit		0.894	0.917
Upper Limit		1.155	1.158
Weeks to First Observed Tumor	74	87	48

(a) Dosed groups received 2,500 or 5,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

(g) These tumors include squamous-cell papilloma, squamous-cell carcinoma, trichoepithelioma, sebaceous adenoma, keratoacanthoma and hemangiopericytoma, NOS.

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Dimethyl Terephthalate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Adenoma (b)	3/50 (6)	0/49 (0)	0/50 (0)
P Values (c,d)	P = 0.038 (N)	N.S.	N.S.
Relative Risk (f)		0.000	0.000
Lower Limit		0.000	0.000
Upper Limit		1.696	1.663
Weeks to First Observed Tumor	106	--	--
Hematopoietic System: Lymphoma or Leukemia (b)	8/50 (16)	7/49 (14)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.893	0.375
Lower Limit		0.298	0.067
Upper Limit		2.598	1.460
Weeks to First Observed Tumor	87	61	102

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Pituitary: Chromophobe Adenoma (b)	21/46 (46)	16/46 (35)	19/48 (40)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.762	0.867
Lower Limit		0.434	0.517
Upper Limit		1.322	1.455
Weeks to First Observed Tumor	87	92	85
Thyroid: C-cell Carcinoma (b)	0/50 (0)	2/49 (4)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		Infinite	Infinite
Lower Limit		0.302	0.601
Upper Limit		Infinite	Infinite
Weeks to First Observed Tumor	--	105	104

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Thyroid: C-cell Carcinoma or Adenoma (b)	1/50 (2)	3/49 (6)	3/50 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		3.061	3.000
Lower Limit		0.256	0.251
Upper Limit		157.341	154.270
Weeks to First Observed Tumor	106	105	104
Mammary Gland: Fibroadenoma (b)	17/50 (34)	12/49 (24)	7/50 (14)
P Values (c,d)	P = 0.013 (N)	N.S.	P = 0.017 (N)
Relative Risk (f)		0.720	0.412
Lower Limit		0.353	0.159
Upper Limit		1.423	0.944
Weeks to First Observed Tumor	106	97	85

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Uterus: Endometrial Stromal Polyp (b)	10/48 (21)	10/48 (21)	6/49 (12)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.000	0.588
Lower Limit		0.412	0.190
Upper Limit		2.427	1.638
Weeks to First Observed Tumor	95	105	105
Uterus: Endometrial Stromal Polyp or Sarcoma (b)	11/48 (23)	11/48 (23)	8/49 (16)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.000	0.712
Lower Limit		0.436	0.273
Upper Limit		2.293	1.769
Weeks to First Observed Tumor	95	102	78

Table E2. Analyses of the Incidence of Primary Tumors in Female Rats Administered Dimethyl Terephthalate in the Diet (a)

(continued)

(a) Dosed groups received 2,500 or 5,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX F

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS IN MICE ADMINISTERED DIMETHYL TEREPHTHALATE IN THE DIET

Table Fl. Analyses of the Incidence of Primary Tumors in Male Mice Administered Dimethyl Terephthalate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Integumentary System: Fibroma (b)	3/50 (6)	5/49 (10)	3/49 (6)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.701	1.020
Lower Limit		0.351	0.143
Upper Limit		10.426	7.273
Weeks to First Observed Tumor	86	102	105
Integumentary System: Fibrosarcoma (b)	11/50 (22)	8/49 (16)	9/49 (18)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.742	0.835
Lower Limit		0.283	0.336
Upper Limit		1.846	2.014
Weeks to First Observed Tumor	86	85	81

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma (b)	1/49 (2)	1/49 (2)	6/49 (12)
P Values (c,d)	P = 0.023	N.S.	N.S.
Relative Risk (f)		1.000	6.000
Lower Limit		0.013	0.769
Upper Limit		76.918	269.767
Weeks to First Observed Tumor	104	105	105
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	1/49 (2)	8/49 (16)	13/49 (27)
P Values (c,d)	P = 0.001	P = 0.015	P less than 0.001
Relative Risk (f)		8.000	13.000
Lower Limit		1.137	2.085
Upper Limit		346.538	537.589
Weeks to First Observed Tumor	104	84	105

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Hematopoietic System: Lymphoma or Leukemia (b)	7/50 (14)	1/49 (2)	4/49 (8)
P Values (c,d)	N.S.	P = 0.032 (N)	N.S.
Relative Risk (f)		0.146	0.583
Lower Limit		0.003	0.133
Upper Limit		1.073	2.139
Weeks to First Observed Tumor	77	105	102
All Sites: Hemangiosarcoma (b)	2/49 (4)	4/49 (8)	0/49 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		2.000	0.000
Lower Limit		0.302	0.000
Upper Limit		21.298	3.379
Weeks to First Observed Tumor	102	81	--

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
All Sites: Hemangiosarcoma or Hemangioma (b)	3/49 (6)	6/49 (12)	0/49 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Departure from Linear Trend (e)	P = 0.028 (N)		
Relative Risk (f)		2.000	0.000
Lower Limit		0.455	0.000
Upper Limit		11.748	1.662
Weeks to First Observed Tumor	102	81	--
Liver: Hepatocellular Carcinoma (b)	17/49 (35)	13/49 (27)	15/49 (31)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.765	0.882
Lower Limit		0.386	0.466
Upper Limit		1.481	1.655
Weeks to First Observed Tumor	93	102	61

Table F1. Analyses of the Incidence of Primary Tumors in Male Mice Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma or Adenoma (b)	19/49 (39)	13/49 (27)	16/49 (33)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.684	0.842
Lower Limit		0.353	0.464
Upper Limit		1.288	1.512
Weeks to First Observed Tumor	93	102	61

(a) Dosed groups received 2,500 or 5,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Dimethyl Terephthalate in the Diet (a)

Topography: Morphology	Matched Control	Low Dose	High Dose
Lung: Alveolar/Bronchiolar Carcinoma or Adenoma (b)	4/48 (8)	5/50 (10)	0/49 (0)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		1.200	0.000
Lower Limit		0.275	0.000
Upper Limit		5.712	1.056
Weeks to First Observed Tumor	105	105	--
Hematopoietic System: Lymphoma (b)	16/48 (33)	5/50 (10)	27/49 (53)
P Values (c,d)	P = 0.014	P = 0.005 (N)	P = 0.025
Departure from Linear Trend (e)	P less than 0.001		
Relative Risk (f)		0.300	1.653
Lower Limit		0.094	1.000
Upper Limit		0.780	2.782
Weeks to First Observed Tumor	87	87	75

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Liver: Hepatocellular Carcinoma (b)	5/48 (10)	1/50 (2)	0/49 (0)
P Values (c,d)	P = 0.010 (N)	N.S.	P = 0.027 (N)
Relative Risk (f)		0.192	0.000
Lower Limit		0.004	0.000
Upper Limit		1.630	0.776
Weeks to First Observed Tumor	98	105	--
Pituitary: Chromophobe Adenoma (b)	3/46 (7)	1/44 (2)	1/49 (2)
P Values (c,d)	N.S.	N.S.	N.S.
Relative Risk (f)		0.348	0.313
Lower Limit		0.007	0.006
Upper Limit		4.142	3.733
Weeks to First Observed Tumor	105	105	89

Table F2. Analyses of the Incidence of Primary Tumors in Female Mice Administered Dimethyl Terephthalate in the Diet (a)

(continued)

Topography: Morphology	Matched Control	Low Dose	High Dose
Ovary: Papillary Cystadenoma, NOS (b)	0/47 (0)	3/50 (6)	0/48 (0)
P Values (c,d)	N.S.	N.S.	--
Departure from Linear Trend (e)	P = 0.016 (N)		
Relative Risk (f)		Infinite	--
Lower Limit		0.566	--
Upper Limit		Infinite	--
Weeks to First Observed Tumor	--	105	--

(a) Dosed groups received 2,500 or 5,000 ppm.

(b) Number of tumor-bearing animals/number of animals examined at site (percent).

(c) Beneath the incidence of tumors in the control group is the probability level for the Cochran-Armitage test when P is less than 0.05; otherwise, not significant (N.S.) is indicated. Beneath the incidence of tumors in a dosed group is the probability level for the Fisher exact test for the comparison of that dosed group with the matched-control group when P is less than 0.05; otherwise, not significant (N.S.) is indicated.

(d) A negative (N) indicates a lower incidence in a dosed group than in a control group.

(e) The probability level for departure from linear trend is given when P is less than 0.05 for any comparison.

(f) The 95% confidence interval of the relative risk between each dosed group and the control group.

APPENDIX G

ANALYSIS OF DOSED DIETS FOR CONCENTRATIONS OF DIMETHYL TEREPHTHALATE

APPENDIX G

Analysis of Dosed Diets for Concentrations of Dimethyl Terephthalate

Duplicate 4-g samples of dosed diets were agitated with 10 ml of benzene and aliquots of the supernatant were analyzed by gas chromatography using a flame ionization detector. Spiked samples and a feed blank were worked up simultaneously with the dosed feed samples. All assays of dosed feed samples were corrected for recovery losses. These analyses were performed at Hazleton, and the results are tabulated below.

Theoretical Concentrations (ppm)	No. of Samples	Sample Analytical Mean (ppm)	Coefficient of Variation (%)	Range (ppm)
2,500	7	2391	5.38	2120-2513
5,000	6	4912	5.72	4482-5297

Review of the Bioassay of Dimethyl Terephthalate* for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

December 13, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute on the Institute's bioassay program to identify and evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, and State health officials. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of Dimethyl Terephthalate.

The primary reviewer for the report on the bioassay of Dimethyl Terephthalate said that the compound was not carcinogenic in either sex of treated rats or in treated female mice. In treated male mice, Dimethyl Terephthalate induced a statistically significant incidence of lung tumors. After a brief description of the experimental design, the reviewer said that the dose levels tested and survival were adequate. Based on the results of the study, he concluded that Dimethyl Terephthalate could be considered to pose "some carcinogenic risk" to human beings.

The secondary reviewer also agreed with the conclusions presented in the report. One Subgroup member questioned the significance of the lung tumors, since an elevated incidence was observed in only one sex.

It was moved that the report on the bioassay of Dimethyl Terephthalate be accepted as written. The motion was seconded and approved without objection.

<u>Clearinghouse Members Present:</u>

Arnold L. Brown (Chairman), University of Wisconsin Medical School
Joseph Highland, Environmental Defense Fund
William Lijinsky, Frederick Cancer Research Center

Henry Pitot, University of Wisconsin Medical Center
Verne A. Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical USA
Michael Shimkin, University of California at San Diego
Louise Strong, University of Texas Health Sciences Center
Kenneth Wilcox, Michigan State Health Department

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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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NIH Publication No. 79-1376